Efficacy of Posaconazole Prophylaxis in Patients with Acute Myeloid Leukemia Undergoing Induction Chemotherapy: An Observational Study in Resource Limited Settings

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Abstract Large randomized controlled trials have shown significant decrease in incidence of invasive fungal infection in acute myeloid leukemia patients with Posaconazole prophylaxis. However, very less is known about value of Posaconazole prophylaxis in resource limited settings. This observational cohort study evaluated the incidence of fungal infection in patients with hematological malignancies undergoing induction chemotherapy with Posaconazole as antifungal prophylaxis and was compared with historical controls who received Fluconazole as fungal prophylaxis. The study was conducted from Oct 2013 to July 2015 in Department of Hematology of a tertiary care center. Fifty-three patients of acute myeloid leukemia on Posaconazole as fungal prophylaxis and 53 historical controls on Fluconazole as fungal prophylaxis were included for final analysis. Baseline characteristics were well matched between groups. Patients on Fluconazole were more likely to experience breakthrough IFDs (28.3 and 11.3%; $p = 0.028$) than in patients receiving Posaconazole prophylaxis. No significant difference was observed in overall, attributable mortality or in shift to first line antifungal. Both Posaconazole and Fluconazole were well tolerated with no major adverse effects requiring discontinuation of the drug. Minor side effects were seen in 39 and 47% patients in study and control group respectively. Vomiting and nausea were the commonest side effects seen in both study and control group (26 vs. 34% and 38 vs. 40% of patients, respectively). The results of our study in patients with acute myeloid leukemia provide

evidence that Posaconazole prophylaxis significantly decreases the incidence of fungal infection and is well tolerated.

Keywords Antifungals · Triazoles · Prophylaxis · Neutropenia · Invasive fungal infections

Introduction

Patients of Acute Myeloid Leukemia (AML) are at a high-risk for invasive fungal disease (IFD) during induction chemotherapy due to prolonged bone marrow aplasia [1]. Invasive fungal diseases (IFDs) are an important cause of morbidity and mortality in AML patients and are associated with high management cost and overall significant economic burden. Antifungal prophylaxis is the standard treatment strategy for the prevention of IFDs [2].

Many antifungals have been used for prophylaxis. These include Fluconazole, Itraconazole and Posaconazole. In most of the developing countries Fluconazole has been used as the standard antifungal prophylaxis. Fluconazole is a cheap and well tolerated drug but with efficacy only against candida. Itraconazole has efficacy against aspergillus but has issues related to oral preparation and absorption. Posaconazole has been a recent entry in this segment.

As per the current guidelines antifungal prophylaxis with Posaconazole is recommended as it has demonstrated a decrease in IFIs and an overall survival benefit compared with fluconazole in patients with AML induction [3]. Insufficient Indian data is available on the use of Posaconazole antifungal prophylaxis. In addition, its high cost limits its widespread availability in the Indian setting.

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This study analyzed the clinical efficacy and tolerability of Posaconazole, which is the recommended antifungal prophylaxis agent as per current guidelines, in the Indian setting and compared with historical data related to use of alternative drug as antifungal prophylaxis i.e. Fluconazole in this setting.

Materials and Methods

We conducted an observational cohort study from Oct 2013 to April 2015 with an aim to study the effectiveness of Posaconazole as fungal prophylaxis in patients of Acute Myeloid Leukemia receiving induction chemotherapy in Indian population. The inclusion criteria included all newly diagnosed patients of Acute Myeloid Leukemia of more than 13 years age and admitted for induction chemotherapy with no evidence of baseline fungal infection, renal, hepatic or cardiac dysfunction. Historical patients of Acute Myeloid Leukemia who received Fluconazole as fungal prophylaxis during induction chemotherapy were used as controls in this study. The exclusion criteria included any patient with evidence of fungal infection (positive radiological findings or/and positive galactomannan), patients with preexisting renal dysfunction (estimated creatinine clearance less than 20 mL/min at baseline or likely to require dialysis during the study), hepatic dysfunction (aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase levels greater than 5 times the upper limit of normal (ULN), or a total bilirubin level greater than 3 times the ULN) or prolonged QTc interval by manual reading (QTc greater than 450 ms for men and greater than 470 ms for women), and pregnant or nursing female patients. Also, patients who were on any drug already known to have interaction with azoles were excluded from the study.

The study group baseline data (before start of chemotherapy) included patient characteristics, primary diagnosis, cytogenetics (Risk stratification on basis of cytogenetics), CT chest, serum galactomannan, duration of symptoms, date of admission, date of starting chemotherapy and date of starting Posaconazole prophylaxis.

The study group patients received 200 mg of Posaconazole as an oral suspension three times daily along with a fatty meal and control group patients received 400 mg of Fluconazole as oral tablet. Enrolled patients during the study period were followed till the end of induction. Data of Historical controls was retrieved from Medical records. The patients were studied for duration of antifungal prophylaxis, side effects (major/minor) due to drug intake, (minor side effects: not requiring discontinuation of the drug, major side effects: requiring discontinuation of drug), duration of fever before stopping

antifungal prophylaxis, second line antifungal drug used, reasons for shifting to second line antifungal. The fungal infection was defined as per EORTC/MSG Consensus group as Proven (fungus detected by histological analysis or culture of a specimen of tissue taken from a site of disease) and probable (host factor that identified patients at risk, clinical signs and symptoms consistent with disease entity and mycological evidence that encompassed culture and microscopic analysis but also indirect test such as antigen analysis). Prior studies done in the Department of Microbiology at our institute had shown a Sensitivity and Specificity of Serum Galactomannan to predict a fungal infection at a GM index of > 0.5 as 100 and 45% respectively. At GM index of > 1 the sensitivity and specificity increased to 98 and 92% respectively. Thus, a cut off of > 1 was taken for Positive Serum Galactomannan in the present study. Day + 14 bone marrow was done as per standard protocol and outcome was defined at D + 28 as complete remission, no complete remission or death.

Primary Analysis

The primary efficacy end point was frequency of proven or probable invasive fungal infection during the induction chemotherapy and frequency of death due to invasive fungal infection.

Secondary Analysis

Secondary end points included frequency of discontinuation of antifungal prophylaxis, escalation to empirical antifungal therapy and final outcome of patients.

Safety Analysis

Major and minor adverse events were recorded and analysed for both the groups.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software (version 16, SPSS, Inc, Chicago, IL, USA). Continuous and categorical variables were displayed as median (inter-quartile range) and proportions/percentages, respectively. The Mann–Whitney *U* test was used to assess the differences between the test group (treated with Posaconazole prophylaxis) and the control group (historical cohort treated with Fluconazole). Differences between categorical variables were analyzed by Chi square test. *P* values < 0.05 were considered to be statistically significant.

Results

A total of 95 patients were recruited in the study group during the study period from Oct 2013 to July 2015. However, for the final analysis a total of 42 patients were excluded as they did not fulfil the inclusion criteria. Fifteen patients were excluded as baseline galactomannan was not available, 04 patients were excluded because of baseline evidence of fungal pneumonia, 23 patients were excluded from the study because of delayed (≥ 7 days from admission) start of posaconazole prophylaxis. Finally, 53 patients of which 26 were males and 27 were females, were included in the result analysis. The demographic characteristics of the study group is given in Table 1.

Medical Records of 38 patients who received Fluconazole as fungal prophylaxis during the period from 2011 to 2012 were retrieved from Medical Record Department. 15 patients during the study period who received Fluconazole as antifungal prophylaxis were also included in the control group. Hence, a total of 53 patients were included in the control group. Serum Galactomannan and baseline CT was not done routinely as baseline investigation to assess fungal infection during that period. Hence, baseline CT scan and Serum Galactomannan was not available for all patients. All patients included in the control group had no clinical evidence of fungal infection and had a normal baseline chest X-ray. Patients in the study and control group were matched for various characteristics like age and gender (Table 1).

Study and control group were matched for median duration of symptoms (2 vs. 1.5 months, $p = 0.258$), primary diagnosis ($p = 0.37$), risk stratification based on cytogenetics ($p = 0.812$), median duration of start of chemotherapy from admission (6 vs. 5, $p = 0.30$) and Day + 14 marrow (M1:M2:M3:ND = 33:9:4:7 vs. 36:3:8:5, $p = 0.14$) (Table 1).

Significant difference was noted between study and control group in number of patients treated in General ward (55 vs. 74%, $p = 0.03$) and in median duration of start of fungal prophylaxis (3 vs. 1 day, $p < 0.01$) (Table 1).

Primary Outcome

Breakthrough IFD occurred in 6 patients (6 of 53, 11.3%) in study group and 15 patients (15 of 53, 28.3%) in control group ($p = 0.02$). Frequency of invasive fungal infection was significantly higher in fluconazole group (Table 1). In the study group 1 patient had proven IFD (Cunningmella fungal sinusitis proved on nasal swab culture) and 5 patients had probable IFD (Fungal pneumonia). In the control group all 15 patients had Probable IFD. 1 patient had Liver involvement and rest 14 patients had Fungal

pneumonia. 1 (1.9%) patient died due to IFD in study group, whereas, 4 (7.5%) patients died in control group due to IFD ($p = 0.36$) (Table 1).

Secondary Outcomes

Overall discontinuations, for any reason were almost equal in both the groups (64 vs. 68%, $p = 0.54$). Escalation to empirical antifungal therapy (EAFT) was the most common reason for discontinuation of antifungal prophylaxis (29 vs. 25). A possible/probable (positive serology and/or CT findings suggestive of fungal infection) lead to discontinuation of antifungal prophylaxis in 5 (15%) patients in Posaconazole group and 11 (21%) patients in control group. Amphotericin B was the most frequently used therapeutic antifungal in both study and control group (71 vs. 69%) (Table 1).

No major adverse effects requiring cessation of drug in either of the group were seen. Minor adverse events were seen in 39% patients in study group and 47% in control group, the difference was statistically insignificant ($p = 0.43$) (Table 1). Nausea and vomiting were the commonest side effects seen in both the groups (20 and 14 vs. 21 and 18). It needs to be mentioned, nausea and vomiting could also be due to chemotherapeutic agents given during induction and mucositis. Other minor side effects were abdominal pain (5 vs. 5), transient rise in bilirubin (1 vs. 8), dizziness (1 vs. 1) and diarrhea (0 vs. 2) (Table 1).

Final outcome of patients was statistically insignificant among study and control groups ($p = 0.39$). Complete remission was achieved in 36 (68%) vs. 31 (58%) patients, whereas, 6 (11%) vs. 11 (21%) did not achieve complete remission. 11 patients died in both groups during induction chemotherapy (Table 1).

Discussion

Patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) who undergo successive cycles of myelosuppressive chemotherapy or who undergo hematopoietic stem cell transplantation (HSCT) have a high incidence of proven and probable mould and yeast infections [3].

The two commonly used approaches to preventing fungal infections in patients undergoing induction chemotherapy are environment control in the form of use of reverse isolation (laminar airflow and HEPA filtered rooms) and antifungal chemoprophylaxis. Reverse isolation has been shown to reduce the incidence of infections, however the impact on survival is not clear. This study was carried out at a tertiary care hospital in a developing

Table 1 Patient demographics, Primary outcomes and Secondary outcomes

Characteristic	Study group (n = 53) n (%)	Control group (n = 53) n (%)	P value
Median age (years)	31 (13–63)	22 (13–65)	0.07
Gender (M:F)	26:27	34:19	0.11
Median duration of symptoms before admission (months)	2 (0–6)	1.5 (0–6)	0.258
Primary diagnosis			0.37
Primary AML	49 (92)	49 (92)	
MDS related AML	1 (2)	2 (4)	
MPAL	3 (6)	2 (4)	
Cytogenetic risk stratification (NCCN)			0.812
Good risk	5 (9.4)	8 (15)	
Intermediate risk	34 (64)	33 (62)	
High risk	3 (5.6)	2 (3.7)	
Not known	11 (21)	10 (19.3)	
Type of ward (general:private)	29:24 (55:45)	39:14 (74:26)	0.04
Median duration of start of fungal prophylaxis from admission	3 (1–6)	1 (1–2)	<0.01
Median duration of start of Chemotherapy from admission	6 (1–7)	5 (1–7)	0.30
Median duration of fungal prophylaxis	24 (6–46)	18 (6–39)	0.02
Minor adverse effects			0.43
Nausea	20 (38)	21 (40)	
Vomiting	14 (26)	18 (34)	
Abdominal pain	5 (9)	5 (9)	
Transient rise in bilirubin	1 (1.9)	8 (15)	
Dizziness	1 (1.9)	1 (1.9)	
Diarrhoea	0 (0)	2 (3)	
Major adverse effects	0	0	
Shift to therapeutic antifungal	34 (64)	36 (68)	0.54
Empirical	29 (85)	25 (69)	
Possible/probable	5 (15)	11 (31)	
Therapeutic antifungal			0.55
Amphotericin B	24 (71)	25 (69)	
Voriconazole	8 (24)	11 (31)	
Caspofungin	2 (5)		
Day + 14 marrow			0.14
M1	33 (62)	36 (68)	
M2	9 (17)	3 (5)	
M3	4 (7)	8 (15)	
Not done	7 (14)	5 (12)	
Frequency of invasive fungal	6 (11.3)	15 (28.3)	0.02
Infection (probable + proven)	(5 + 1)	(15 + 0)	
Outcome			0.39
CR	36 (68)	31 (58)	
NCR	6 (11)	11 (21)	
Expired	11 (21)	11 (21)	
Death due to fungal pneumonia	1 (1.9)	4 (7.5)	0.36

country in resource limited setting [4]. Patients receive induction chemotherapy for AML in general or private

wards and the environment control as discussed above is not available in our setting.

Antifungal prophylaxis with fluconazole reduces morbidity and mortality among recipients of allogeneic hematopoietic stem-cell transplants and chemotherapeutic regimens who have prolonged neutropenia [5, 6]. Fluconazole prophylaxis is also used in other patient populations with neutropenia, although fewer data support its efficacy in these patients. Fluconazole has an acceptable adverse-event profile but lacks efficacy against filamentous fungi, which have become increasingly frequent causes of infection in patients with neutropenia [7].

In our center adoption of Posaconazole in comparison to Fluconazole prophylaxis in a high risk cohort of AML patients was associated with a significant decrease in frequency of breakthrough invasive fungal infections (28.3 vs. 11.3%, $p = 0.02$). The incidence of IFD in AML patients undergoing intensive chemotherapy at our center appears to be high compared to that reported for some recent multicenter studies. Oliver A Cornely [8] in a study of 304 patients, found the incidence of breakthrough fungal infection as 2%, while Ananda-Rajah et al. [2] in their retrospective study of 516 Posaconazole prophylaxis courses found it to be 3%. In a small cohort of 24 patients but with monitored serum Posaconazole levels, Paola Minetto et al. [9] found no breakthrough fungal infections. Hsiang-Chi Kung et al. from Taiwan (2014), in their cohort of 130 patients found fungal infection in 9.2% patients [10] and incidence of IFD was 23.2% in study conducted by Girmenia et al. from Italy [11]. These studies were conducted outside the control setting, almost similar to a ‘real-world’ setting [10, 11].

Several factors need to be considered. Posaconazole is available in only a liquid form and needs administration with a high fat diet. Despite this the GI absorption and the bioavailability of Posaconazole has been a concern and is best monitored by serum Posaconazole levels [12]. Although administration of Posaconazole in the study cohort was strictly monitored as per the recommendations for administration [10], serum Posaconazole levels were not monitored in this study. This limitation could possibly explain to a certain extent the variance in the results. Most of the data mentioned above represents western literature where stringent environment control is practiced/available for patients undergoing induction chemotherapy for AML [2, 8, 9]. In the absence of reverse isolation barrier the incidence of fungal infection is likely to go up significantly [4]. The dynamics of the interaction of an uncontrolled environment and antifungal prophylaxis effects in these neutropenic patients is unknown. In the absence of any concrete data from developing countries where induction chemotherapy to AML patients is given in general/private wards, our data possibly represents the first such data on the incidence of fungal infection in the setting of antifungal

prophylaxis with documented absence of fungal infection at baseline.

Still the finding of a significant reduction in fungal infections in the Posaconazole cohort points to the fact that it is able to overcome these limitations of environmental control to some extent. Also, the costs of a neutropenic setup for induction chemotherapy may not be feasible in the setting of a developing country. This may justify the cost of Posaconazole and it may be economically prudent in the real world developing country setting.

With 11.3% of the patients developing documented fungal infection, but an induction mortality attributable to fungal infection of 2%, indicates that the use of therapeutic antifungals at breakthrough was effective enough to prevent mortality due to fungal infection in a significant number of patients at D + 30 on induction chemotherapy. This is attributable to early and aggressive, albeit sometimes without enough serological/radiological evidence, use of therapeutic antifungals which is guided by the physician discretion.

Cornely et al. [8] demonstrated significantly improved survival in patients on Posaconazole prophylaxis as compared to Fluconazole group. This was out of scope of the present study to assess survival benefit. The mortality attributable to fungal infection was 2% in the Posaconazole group while it was 7% in the Fluconazole group. Although, there was lesser attributable mortality in the Posaconazole group this did not reach statistical significance (0.36). This is a very important finding that there is a trend towards reduced mortality attributable to fungal infection in the Posaconazole group although it has not reached statistical significance. It is noteworthy that most of the studies have not reported on the induction mortality specifically attributable to fungal infections during induction chemotherapy, especially in patients receiving antifungal prophylaxis. This may be one of the first studies demonstrating fungal infection attributable mortality.

Oliver A Cornely et al. [8] noted with concern the possibility of a decreased ejection fraction, prolongation of the QT or QTc interval, and torsades de pointes, possibly related to Posaconazole. However, in our study both Posaconazole and Fluconazole were found to be well tolerated. No major side effect requiring discontinuation of antifungal prophylaxis was seen in either of the groups. Minor side effects were more common with Fluconazole but did not reach statistical significance (p value = 0.43).

Conclusion

Posaconazole as fungal prophylaxis in comparison to Fluconazole prophylaxis significantly reduced the frequency of IFD even in resource limited settings. Thus,

Posaconazole is useful along with standard care for patients with AML undergoing induction chemotherapy.

Limitations of the Study

There was a significant difference in median age of patients and number of patients treated in general in study and control group. Baseline Galactmanan levels and CT scan was not available in all the historical controls. A randomized clinical trial would have given a more robust evidence in support of Posaconazole as fungal prophylaxis. Instead of historical control, simultaneous recruitment of patients in the study as control would have eliminated the bias of having different patient profile, diagnostic criteria and environmental factors. Posaconazole levels were not done to assess bioavailability of Posaconazole.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval Ethical clearance was taken from the Institutional ethics committee.

Informed Consent Informed consent was taken from all the participants of this study.

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