Breakthrough Invasive Fungal Infections based on *CYP2C19* Enzyme in Patients Who were on Voriconazole (VRC) as Primary Antifungal Prophylaxis in Acute Myeloid Leukemia (AML) undergoing Induction Chemotherapy

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Abstract

Background: Voriconazole (VRC) is metabolized predominately by polymorphic *CYP2C19* enzyme to metabolites with less antifungal potency. There has been a great interest in understanding *CYP2C19* enzyme activity on voriconazole and its effect on breakthrough invasive fungal infections (bIFI)*.

Methods: Retrospective chart review of patients undergoing induction chemotherapy+ for AML at a single NCI designated cancer center who are getting VRC for fungal prophylaxis. *CYP2C19* guided recommendations were as following: avoidance of VRC in ultra rapid metabolizers, VRC 300 mg twice daily (BID) for rapid metabolizers, and VRC 200 mg BID for all other phenotypes

Results: 89 patients received VRC for primary prophylaxis, of which 19 were rapid, 34 were normal, 14 were intermediate, 3 were poor metabolizer phenotypes and 19 had no data on *CYP2C19* genotype. bIFI occurred in 20.2% (18/89) patients on VRC. Of the patients with bIFI infections, 15.7% (3/19) of patients were rapid metabolizers, 14.7% (5/34) were normal metabolizers, 28.5% (4/14) were intermediate metabolizers and 0% (0/3) were poor metabolizers. There were 31% (6/19) breakthrough infections in patients with unknown *CYP2C19* genotype.

Conclusions: There is no significant statistical difference among *CYP2C19* enzyme activity categories with respect to breakthrough of invasive fungal infections. However, obtaining *CYP2C19* genotype prior to VRC therapy allows for dosing optimization and possibly reduction of bIFI.

Introduction

VRC is often used for prophylactic anti-fungal therapy in induction chemotherapy for AML patients due to predictable absorption and an extended spectrum antifungal activity.

VRC is metabolized predominately by *CYP2C19* enzyme to metabolites with less antifungal activity. There has been a great interest in understanding the role of *CYP2C19* as it significantly affects drug metabolism and pharmacokinetics of numerous drugs including voriconazole. Approximately 39% of patients are genetically predicted to be *CYP2C19* ultra-rapid or rapid metabolizers and thus maybe at an increased risk of sub-therapeutic voriconazole concentrations and may be at increased risk of bIFI [1-4].

This study assesses the incidence of bIFI at Moffitt Cancer Center based on *CYP2C19*-guided dosing

Methods

This is a single-center retrospective analysis of patients who underwent induction chemotherapy for newly diagnosed AML and received VRC as the primary antifungal prophylaxis between July 2017 to June 2019 (see Table 1).

Table 1:

Patient Eligibility/Inclusion Criteria:
Age of ≥ 18 years old
Patients with newly diagnosed AML receiving induction chemotherapy between July 2017 to June 2019
Receiving at least 10 days of uninterrupted primary antifungal prophylaxis with VRC

Table 1 (Continued):

Patient Eligibility/Exclusion Criteria:
Received systematic antifungal therapy (other than fluconazole) within 30 days prior to the initiation of induction chemotherapy
Patients with relapsed or refractory AML
History of stem cell transplantation or cellular therapy (autologous, allogeneic, CAR-T)
History of solid organ transplant
History of HIV
Receiving chemotherapy that is not qualify as induction as per study definition

Per hospital protocol, all patients diagnosed with AML should have *CYP2C19* genotype prior to or within one week of admission.

Based on the results, the patients are categorized as rapid metabolizers, intermediate metabolizers, normal metabolizers, poor metabolizers and unknown *CYP2C19* activity. *CYP2C19* guided recommendations were as following: avoidance of VRC in ultrarapid metabolizers, VRC 300 mg BID for rapid metabolizers, and VRC 200 mg BID for all other phenotypes.

The data was analyzed using Fisher Exact Test. This allowed for comparison of categorical outcome according to different independent groups for small sample sizes.

Results

- 89 patients met the inclusion criteria (19 were rapid, 34 were normal, 14 were intermediate, 3 were poor metabolizer phenotypes and 19 had no data on *CYP2C19* genotype) with the following baseline characteristics (Table 2):

Table 2:

	Baseline Patient Characteristics
Average Age, years	60.2 (range 21 to 79)
Male, n	56
Female, n	33
Average time to bIFI, days	25.4
Mortality in 60 days, n	7
Average dose#	Ultra rapid metabolizers – not included in the study Rapid metabolizers (n=19)-300 mg twice daily Normal metabolizers (n=34)-200 mg twice daily Intermediate metabolizers (n=14)-200 mg twice daily Poor metabolizers (n=3)-200 mg twice daily Unknown CYP2C19 genotype (n=19)-200 mg twice daily

#- initial maintenance dose, patients were then followed up with VRC levels after which doses may have been adjusted

- In this study, there were 18 bIFI out of the 89 patients who received VRC (Figure 1):
  - 15.7% of patients (n=3) who were rapid metabolizers (n=19) had bIFI
  - 14.7% of patients (n=5)who were normal metabolizers (n=34) had bIFI
  - 28.5% of patients(n=4) who were intermediate metabolizers (n=14) had bIFI
  - 0% bIFI (n=0) occurred in poor metabolizers (n=3)
  - 31% of patients (n=6) who had unknown *CYP2C19* characteristics (n=19) had bIFI
  - All the proven cultures grew *Fusarium*
- There is no significant statistical difference (p=0.6) among *CYP2C19* enzyme activity categories with respect to bIFI.

Figure 1:

CYP2C Enzyme Activity Category (Allele) Number (n) of bIFI by possible, probable or proven subset	Percent of bIFI
Rapid Metabolizers (*1/*17) possible bIFI: n=2, no probable and n=1 proven bIFI	15.7 %
Normal Metabolizers (*1/*1) possible bIFI: n=4, no probable and n=1 proven bIFI	14.7%
Intermediate metabolizers (*1/*2, *1/!3, *2/*17, *3/*17) possible bIFI: n=4, no probable or proven bIFI	28.5%
Poor Metabolizers (*2/*2, *3/*3, *2/*3) No of possible, probable or proven bIFI noted	0%
Unknown CYP2C19 (Not Applicable) possible bIFIs: n=4, probable bIFIs: n=1, n=1 proven bIFI	31%

Conclusions

- Given the severity of illness in patients with invasive fungal infections, it is critical that therapeutic VRC concentrations are attained to prevent adverse outcomes.
- We found no statistical difference between *CYP2C19* enzyme activity categories with respect to break through of invasive fungal infections on VRC likely due to the dose adjustments made based on *CYP2C19* activity. However, even with no statistical difference *CYP2C19* should be done to evaluate for ultra-metabolizers as voriconazole should be avoided in these patients.
- However, there are a high number of breakthrough fungal infections in unknown *CYP2C19* enzyme activity category. This group seems to of received the standard VRC 200mg twice daily which may be inadequate if they had rapid or ultra metabolizers.
- For all the categories that had bIFI, most of the bIFI were categorized as possible bIFIs. These patients were empirically started on liposomal amphotericin B.
- One limitation of the study is the lack of analysis of confounding factors. Patients who are being co- administered with other agents that interfere with *CYP2C19* such as pantoprazole. Pantoprazole is often given during inpatient admissions to prevent stress ulcers. Previous *in vivo* and *in vitro* studies demonstrate that proton pump inhibitors increase voriconazole levels. Another example, most aplastic anemia patients are are on Cyclosporine which can interfere with *CYP2C19* as well. Therefore, close monitoring of voriconazole levels is recommended.
- Further studies should be done with a larger sample size to analyze the VRC levels at 5 to 7d to ensure steady state mirrors the genetic testing.

Definitions/References

Disclosure:

None of the authors have financial relationships to disclose with regard to this study.

Definitions for the purpose of this study:

- (+)Induction therapy: Patients receiving 1st cycle of intensive remission chemotherapy after diagnosis with curative intent
- (*) Any patient who required treatment with liposomal amphotericin B, echinocandin, and/or different triazole and met the definition of break though fungal infection as based on The European Organization for Research and Treatment of Cancer/ Invasive Fungal Infection Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group criteria was used to categorize incidence of breakthrough invasive fungal infections (bIFI) into 'possible', 'probable' or 'proven' groups.

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