Breakthrough Invasive Fungal Infections with Isavuconazonium Sulfate (ISA) versus Voriconazole (VRC) as Primary Antifungal Prophylaxis in Patients with Acute Myeloid Leukemia (AML) who Received Induction Chemotherapy

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Abstract

Background: The newer generation triazole antifungal agents, Voriconazole (VRC) and Isavuconazonium sulfate (ISA), have emerged as agents in the prophylactic setting in high-risk AML. This analysis aims to compare the rates of breakthrough invasive fungal infections (bIFI),* in AML patients receiving induction chemotherapy+, who have received VRC or ISA as primary antifungal prophylaxis.

Methods: Retrospective chart review of patients undergoing induction chemotherapy for AML at a single NCI designated cancer center.

Results: There was a 20.2% (18/89) breakthrough rate of bIFI in the VRC arm and 17.2% (5/29) in the ISA arm.

Conclusions: There is no statistical difference (p=1) between VRC and ISA. ISA appears to be as effective as VRC for primary antifungal prophylaxis against bIFI.

Introduction

Fungal infections in patients with hematologic malignancies are associated with high mortality. The newer generation triazole antifungal agents VRC, posaconazole (POS) and ISA, have emerged as agents in the prophylactic setting in high-risk AML undergoing induction chemotherapy+. Recent data have highlighted the emergence of breakthrough invasive fungal infections (bIFI) in patients receiving triazole prophylaxis. Incidence of proven or probable bIFI with POS, VRC and ISA are 3.3%, 2.1%, and 4.6% respectively [1-3].

There are notable differences and limitations between the products. All three have similar and broad spectrum of activity against yeasts and molds but VRC lacks activity against *Mucormycosis*, an emerging fungal pathogen in this patient population. VRC and POS require therapeutic drug monitoring (TDM) and VRC may also require *CYP2C19* enzyme evaluation prior to initiation of therapy given patient variability on drug metabolism. Current data suggests that VRC should be avoided in patients who are ultra rapid metabolizers and higher doses should be used in rapid metabolizers[4].

Only POS has Food and Drug Administration approval for prophylaxis of invasive fungal infections in high risk hematological malignancies. However, there is greater interest emerging in ISA as primary prophylaxis given its favorable side effect profile and lack of need for TDM.

This retrospective analysis aims to compare the rates of breakthrough invasive fungal infections in acute myeloid leukemia patients undergoing induction chemotherapy, who have received VRC or ISA as primary antifungal prophylaxis.

Methods

This is a single-center retrospective analysis of patients undergoing induction chemotherapy for newly diagnosed AML, who received either VRC or ISA as the primary antifungal prophylaxis at Moffitt Cancer Center and Research Institute from July 2017 to June 2019 (Table 1). Statistical analysis was done using the Fisher Exact Test Statistic.

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 either VRC or ISA

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

Results

- 250 patients were screened for the study and out of which 118 patients met the above criteria with the following baseline characteristics (Table 2).

Table 2:

	Voriconazole (n=89)	Isavuconazonium (n=29)
Average Age, years	60.2 (range 21 to 79)	62.9 (range 41 to 77)
Male, n	56	14
Female, n	33	15
Average time to bIFI, days	25.4	19.8
Mortality in 60 days, n	7	3
Average dose#	300 mg twice daily for rapid metabolizers (n=19). 200 mg twice daily for others	372 mg daily

#Average dose doesn't include loading doses. Ultra rapid metabolizers phenotype were excluded from getting VRC.

- There was a 20.2% (18/89) overall break through rate of bIFI in the VRC arm and 17.2% (5/29) in the ISA arm (p=1) (Figure 1). Of these there are:
  - Possible bIFI: VRC 15 (16.8%) vs ISA 2 (6.8%)
  - Probable bIFI: VRC 0 (0%) vs ISA 1 (3.4%)
  - Proven bIFI: VRC 3 (3.3%) vs ISA 2 (6.8%)
    - VRC arm there were 18 total bIFI (Figure 2)
      - 16 pneumonias- cultures grew only in one patient: *Fusarium*
      - 1 bacteremia with pneumonia –cultures grew *Fusarium*
      - 1 toe infection – cultures grew *Fusarium*
    - ISA arm there were 5 total bIFI (Figure 3)
      - 4 pneumonias- cultures grew only in one patient: *Scedosporium*
      - 1 toe infection- cultures grew *Fusarium*
  - Probable + proven bIFI: VRC n=3 (3.3%) vs ISA n=3 (10.2%)

Figure 1:

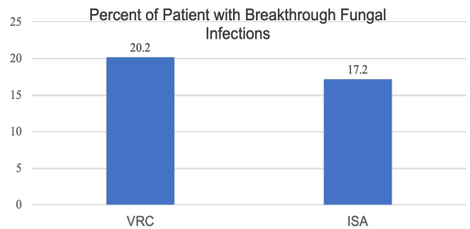


Figure 2:

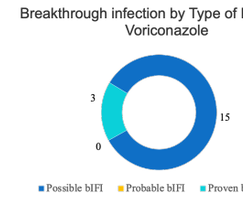
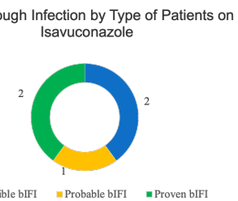


Figure 3:



Conclusions

- In this retrospective study we found no statistical difference in overall bIFI rates between VRC and ISA for primary prophylaxis for AML.
- Based on our findings it appears that ISA can be utilized as an alterative agent for VRC in this setting.
- Most often the bIFI could not be identified and was empirically treated with liposomal amphotericin.
- VRC has several side effects and the most common are hallucinations. Literature has documented altered color sense, photophobia, or blurred vision has occurred in ~30% of patients on VRC [2]. VRC is also known to cause QTc prolongation, photosensitivity in sun exposed areas of the skin. In contrast, ISA has a favorable pharmacokinetic and safety profile and fewer drug–drug interactions.
- Limitations of this study include its retrospective design in a single cancer center. Prospective trial should be done to validate our findings and to assess mortality.

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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