The Real-World Use of Isavuconazole as Primary or Salvage Therapy of Invasive Fungal infections in High-Risk Patients with Hematologic Malignancy or Stem Cell Transplant

Hiba Dagher, MD, Ray Hachem, MD, Anne-Marie Chaftari, MD, Ying Jiang, Shahnoor Ali, Rita Deeba, Shivan Shah, MD, Issam Raad, MD
Department of Infectious Diseases, The University of Texas MD Anderson Cancer Center, Houston

Contact
Hiba Dagher
MD Anderson Cancer Center
hrdagher@mdanderson.org

Introduction

- Invasive fungal infections (IFIs) are a major cause of morbidity and mortality among immunocompromised patients with hematologic malignancies (HM) and stem cell transplants (SCT).
- In 2016, the SECURE trial demonstrated the non-inferior efficacy and fewer drug related adverse effects of Isavuconazole in comparison to voriconazole.
- Isavuconazole was approved by the FDA as a primary therapy for Invasive Aspergillosis (IA) and Mucormycosis.
- **Objective**: To examine the real-world use of Isavuconazole in patients with HM and evaluate their clinical outcomes and safety.

Methods

- A retrospective study of HM patients at MD Anderson Cancer Center who had definite, probable or possible mold infections between April 2016 and January 2020.
- Patients were treated with Isavuconazole for a period of at least 7 days.
- Clinical and radiological findings were assessed at baseline and at 6 and 12 weeks of follow up.
- A **favorable response** was defined as complete or partial resolution. **Failure to respond** was defined as progression or stable response.
- Patients who died within 14 days of Isavuconazole therapy initiation were excluded from the analysis for IFI attributable death.

Results

Table 1. Descriptive Statistics

Characteristics	Patients
	(n=200) N (%)
Age (years), median (range)	63 (20-91)
Sex, male	129 (65)
Type of cancer	
AML	110 (55)
ALL	17 (9)
CLL	6 (3)
CML	10 (5)
Lymphoma	8 (4)
Myeloma	8 (4)
Other cancers	41 (21)
BMT prior to or during IFI	52 (26)
Type of BMT	
Auto	2/52 (4)
Allo	50/52 (96)
GVHD	26/51 (51)
Neutropenia at the onset of IFI	122/200 (61)
Recovery from neutropenia (ANC > 500) during infection	48/122 (39)
Steroids ≥ 600 mg (prednisone equivalent)	55/200 (28)
ICU during infection	86 (43)
Mechanical ventilation during infection	50/198 (25)
Pulmonary co-infection	81 (41)
Use of Isavuconazole as	
Primary therapy	85 (43)
Salvage therapy	115 (58)
Duration of Isavuconazole (days), median (IQR)	48 (21-97)
Monotherapy	59 (30)
Combination	141 (71)
With Polyene	107 (54)
With Echinochandins	53 (27)
Diagnosis of IFI	
Definite	11 (6)
Probable	63 (32)
Possible	126 (63)
Type of infection	
Invasive pulmonary infection	166 (83)
Disseminated infection	11 (6)
Localized infection	17 (8)
Sinus infection	6 (3)
Primary therapy	
Polyene	94 (47)
Voriconazole and/or posaconazole	100 (50)
Isavuconazole	85 (43)
Echinocandins	54 (27)
Salvage therapy	148 (74)
Polyene	59 (30)
Voriconazole and/or posaconazole	47 (24)
Isavuconazole	115 (58)
Echinocandins	45 (23)

Figure 1. Types of IFI

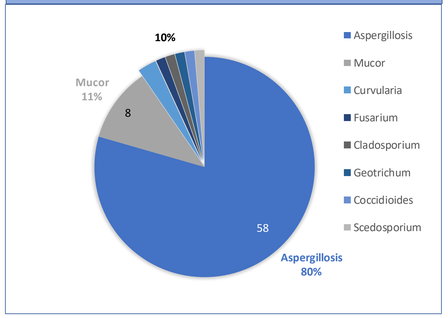


Figure 2. Reasons to Switch to ISA

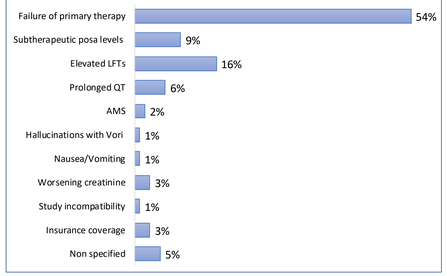


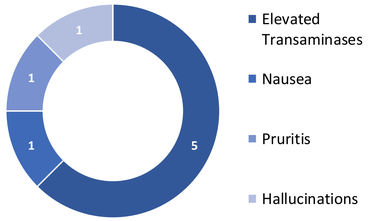
Table 3. Impact of Neutropenia Recovery on ISA Response

Outcomes	Neutropenia recovery	No neutropenia recovery	*p*-value
	(n=48) N (%)	(n=74) N (%)	
Response at week 6			**<.0001**
Favorable response	27/48 (56)	9 (12)	
Failure	21/48 (44)	65 (88)	
All cause mortality at week 6	9 (19)	27/71 (38)	0.025
IFI attributable mortality at week 6	5/44 (11)	18/64 (28)	0.037
Response at week 12			**<.0001**
Favorable response	21/48 (44)	5 (7)	
Failure	27/48 (56)	69 (93)	
All cause mortality at week 12	17/47 (36)	49/71 (69)	0.0004
IFI attributable mortality at week 12	8/41 (20)	39/64 (61)	<.0001

Table 2. Outcomes

Outcomes of Isavuconazole containing regimen	(n=200) N(%)
Response at week 6	
Favorable response	79 (40)
Failure to repsond	121 (60)
Response at week 12	
Favorable response	66 (33)
Failure to repsond	134 (67)
All cause mortality at 6 weeks	49 (25)
IFI-attributable death within 6 weeks	31/190 (16)
All cause mortality at 12 weeks	90 (45)
IFI-attributable death within 12 weeks	63/181 (35)
Outcomes of Isavuconazole monotherapy	**(n=59) N(%)**
Response at week 6	
Favorable response	28 (47)
Failure to repsond	31 (53)

Figure 3. Adverse Events Leading to Discontinuation of ISA



Conclusions

- Selecting Isavuconazole therapy was mainly driven by failure of other antifungal agents, subtherapeutic voriconazole levels or adverse events to other antifungals such as increased LFTs and prolonged QT intervals.
- Isavuconazole seems to be a promising anti-mold therapy and has a good safety profile in high risk cancer patients with HM.
- Recovery of neutropenia during IFI significantly improves the response to Isavuconazole therapy.