A retrospective analysis of antifungal prophylaxis in patients undergoing allogeneic haematopoietic stem cell transplant at a single centre

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Introduction

Despite the significant overall mortality and morbidity burden invasive fungal infections (IFIs) can lead to in allogeneic haematopoietic stem cell transplant (alloHCT) recipients, definitive evidence on the optimal antifungal prophylactic strategies are lacking regarding the choice of drug, associated toxicities, cost effectiveness and timing.

This study evaluated the use of antifungals early post alloHCT with regards to these variables, including the rationale for drug switching where more than one agent is used during a course of treatment.

Aims

1. To map the use of antifungals in alloHCT, and indications were patients change antifungals
2. To determine the frequency of documented antifungal-associated adverse effects, and the adverse effects which result in treatment changes
3. To review the efficacy of the centres antifungal prophylaxis strategy in preventing invasive fungal infections

Methods

A retrospective analysis was undertaken of the antifungal prophylactic strategy for **71** patients at the Royal Adelaide Hospital. All were 16 years or older and had undergone alloHCT between February 2018 and October 2019. Data was collected and analysed from medical records. Baseline patient characteristics and a summary of the centre's alloHCT antifungal prophylaxis guidelines are shown below:

TABLE 1: Patient Characteristics

Patient Characteristics	N
Gender	
Male	45
Female	26
Age (Years)	
16 – 30	6
31 – 50	24
51 – 70	41
Disease	
Acute Myeloid Leukaemia	28
Myelodysplastic syndrome	12
Acute Lymphoblastic Leukaemia	9
Myelofibrosis	9
Other	13
Donor	
Matched Sibling	14
Matched Unrelated	43
Umbilical Cord	9
Haploidentical	5
Conditioning Chemotherapy Intensity	
Myeloablative	17
Midi (cord)	8
Reduced Intensity	46
HCT-CI Score[2]	
0	34
1	17
2	11
≥3	9

FIGURE 1: Antifungal prophylaxis strategy for alloHCT at centre prior to study

1st line: oral posaconazole sustained release tablets

↓

2nd line: intravenous or oral voriconazole

↓

3rd line: intravenous liposomal amphotericin B (Ambisome®)

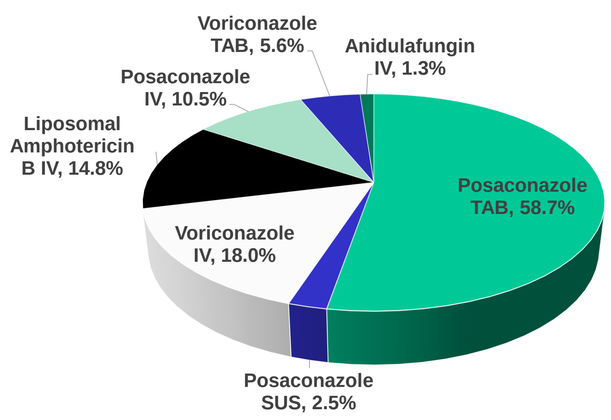
↓

4th line: intravenous posaconazole

Results

SUMMARY OF USE:

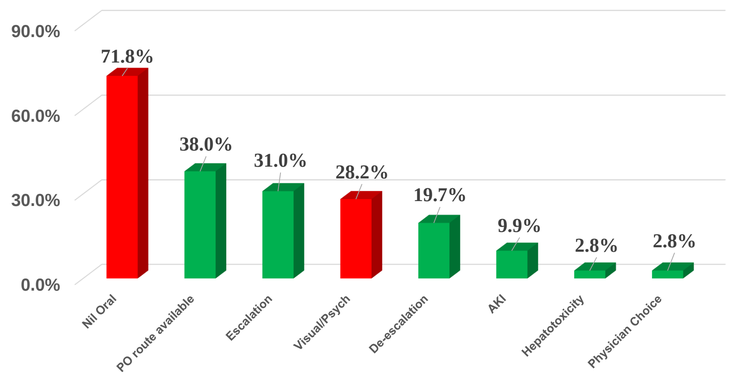
FIGURE 2: Overall Antifungal Exposure



- Only **21% (n=15)** of patients remained on a single antifungal agent (oral posaconazole in all cases)
- The mean number of changes in antifungal per patient was **2.5 (±1.8)** (includes both changes in drug and dosage form)
- The mean numbers of antifungals used per patient were:
  - Different drug only = **2.1 (±0.8)**
  - Different drug and form = **2.6 (±1.1)**

REASONS FOR CHANGE AND ADVERSE EFFECTS:

FIGURE 3: Frequency of reasons for change in antifungal therapy



- The most common adverse events associated with antifungal agents were visual disturbance and delirium
- **49% (n=35)** of patients experienced a neuropsychiatric adverse event defined as visual disturbances, visual hallucinations, auditory hallucinations or delirium
- In **74% (n=26)** of these cases, the adverse event first occurred while patients were on voriconazole
- **77% (20/26)** of patients required changing to an alternative antifungal agent
- The adverse event resolved within 72 hours after ceasing voriconazole in **90% (18/20)** of these patients
- Patients who received voriconazole (n=48) were significantly **(P = 0.013)** more likely to experience a visual/neuropsychiatric event compared to those who did not (n=23)

Results Cont.

THERAPEUTIC DRUG MONITORING:

- Mean voriconazole concentration measured in 17/26 patients experiencing a neuropsychiatric adverse event was **2.2µg/mL (±1.4)***
  **None were above the therapeutic range of 1-5*µg/mL
- Overall, the mean time azole concentrations were within target for each patient was **67.1% (±28%)**

EFFICACY OF ANTIFUNGAL Px:

TABLE 2: Rates of Invasive Fungal Infection

Fungal Infection Category [1]	Number of patients (Proportion)
Possible	**20** (28%)
Probable	**3** (4%)
Proven	**2** (3%)

- **35% (n=25)** of patients were escalated to treatment antifungals
- In **20/25** of these patients, IV Liposomal Amphotericin B was the agent of escalation

Discussion/Conclusions

- Our study showed a significant burden of adverse effects associated with the use of antifungal prophylaxis in alloHCT patients, particularly with voriconazole
- Most patients required the administration of multiple antifungal agents
- A standard antifungal prophylactic strategy utilising the oral modified release tablet and intravenous forms of posaconazole as first line therapy should be evaluated for cost effectiveness to help reduce the side effect burden associated with voriconazole and to decrease exposure to multiple antifungal agents
- After the results of our study, the centre's alloHCT antifungal prophylaxis strategy has changed with intravenous posaconazole now 2nd line, voriconazole 3rd line and intravenous liposomal amphotericin B 4th line.
- An analysis post this change is being undertaken

References

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