Olorofim for a Case of Severe Disseminated *Lomentospora prolificans* infection

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Introduction

- Invasive *Lomentospora prolificans* infection causes significant morbidity and mortality particularly in immunocompromised patients
- Mortality rate is least 65%, and near 100% if infection becomes disseminated[1]

Case Presentation

- A 56-year-old lady diagnosed with T-cell acute lymphoblastic leukemia (T-ALL)
- T-ALL went into remission after HyperCVAD cycle 1a & 1b, but complicated by:

a) Ruptured appendix from neutropenic enterocolitis
b) Disseminated *Lomentospora prolificans* infection (positive blood cultures)
   - Fungal endophthalmitis (Figure 1)
   - Lumbar spine osteomyelitis (L4/ L5 and S1)
   - Presumed pulmonary involvement (Figure 2)

- Isolate was pan-resistant to all antifungals (Table 1)
- Treated with voriconazole (including intravitreal) & terbinafine; unable to attain therapeutic voriconazole level despite augmentation
- Worsening Positron Emission Tomography (PET) uptake in lumbar spine; *L. prolificans* was again isolated from lumbar vertebral biopsy after 3 months of combination therapy → surgical debulking and spine stabilisation surgery
- Developed new palpitations 5 months after spine surgery→ new PET uptake at aortic root and valve
  - Progressive moderate to severe aortic regurgitation on serial echocardiogram
- Eleven months into management, Olorofim was started at loading dose 180mg, followed by 60mg twice daily (BD) and later increased to 90mg BD as guided by drug levels

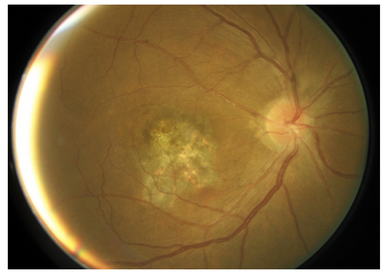

Figure 1. Fungal endophthalmitis

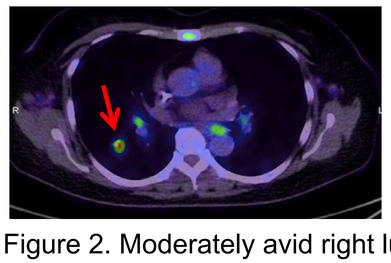

Figure 2. Moderately avid right lung nodule

Antifungal	MIC (µg/mL)
Voriconazole	8
Posaconazole	>8
Anidulafungin	>8
Micafungin	>8
Itraconazole	>16
Fluconazole	>256
5-flucytosine	>64
Amphotericin	>8
Olorofim	0.25

Table 1. MIC of *L. prolificans* to various antifungals

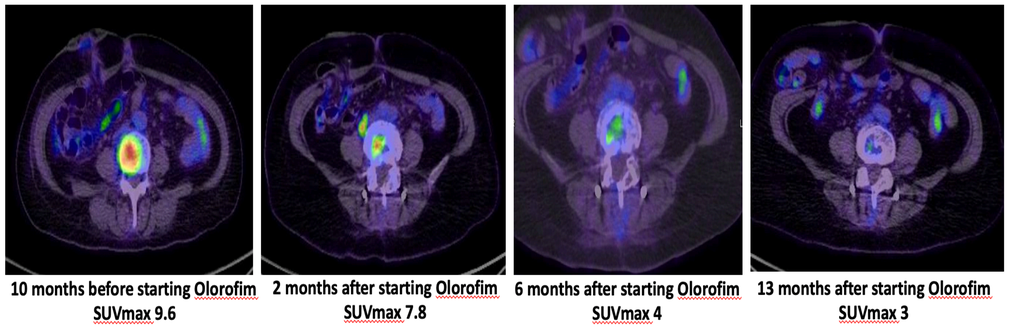

Figure 3. Significant improvement in metabolic uptake at lumbar region L4/5

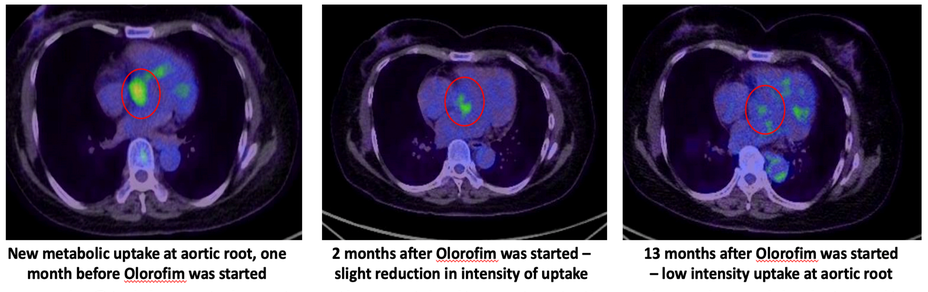

Figure 4. Stable uptake at aortic root in its extent, though reduced in intensity

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Case Presentation (cont.)

- Over the next 12 months, despite relapsed T-ALL needing radiotherapy and chemotherapy, patient did well clinically & significant improvement demonstrated in PET uptake at lumbar spine, with mild improvement of metabolic response in aortic root (Figure 3 & 4)

Discussion

- *Lomentospora* disseminated infection usually occurs in severely immunocompromised hosts following haematogenous spread from lungs, skin or any other source of localised infection[2]
- *L. prolificans* is routinely resistant to all antifungals
- An open-label single-arm phase IIb study of a novel antifungal Olorofim (formerly, F901318) is currently underway – it selectively inhibits fungal dihydro-orotate dehydrogenase, a key enzyme in pyrimidine biosynthesis[3]
- *In vitro* testing in Australia: active against all isolates of *L. prolificans* (30 isolates), with reduction in MICs ranging from 0.125 to 0.5µg/mL[4]
- Olorofim is also active against resistant *Aspergillus* species, *Scedosporium* species, *Coccidioides* and other endemic mycoses, but lacks activity against *Candida*, *Cryptococcus* and *Mucorales* species[5]

Conclusion

- Olorofim monotherapy has demonstrated its potential use in treatment of resistant invasive mould infections in patients lacking suitable alternative treatment options.

References

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