Antifungal Drugs to Address Unmet Medical Need

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Background on Olorofim

• Olorofim
  • Is a novel mechanism candidate antifungal drug\(^1\)
    • It inhibits DHODH (pyrimidine biosynthesis pathway)
  • It shows broad microbiologic activity vs. mould fungi
    • Low MICs vs. *Aspergillus* spp., *Lomentospora prolificans*, *Scedosporium* spp., *Fusarium* spp., *Coccidioides* spp., and others
    • Fungicidal effects in vitro (*Aspergillus*) and in vivo (*Coccidioides*)\(^2,3\)
  • Dosed by mouth (30-mg tablet), it has FDA Breakthrough Therapy Designation based on
    • “preliminary clinical evidence indicating that it may ...”
    • demonstrate substantial improvement over existing therapies ...
    • on one or more clinically significant endpoints.”
  • Now in an open-label Phase 2 study (NCT03583164) of mould IFD\(^4\) in patients with limited treatment options

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4. IFD = Invasive Fungal Disease
Endpoints: A trial design problem

• Day 42 All-Cause Mortality is OK for acute pulmonary IA\(^1\)
  • But it is a blunt tool that gets entangled with underlying disease\(^2\)
  • It doesn’t work at all for infections that progress inexorably but slowly

• EORTC-MSG defined an Overall response endpoint\(^3\)
  • Overall is built from clinical, radiological, & mycological responses
  • Overall Success logically requires improvement on all 3 sub-elements
  • Failure is likewise obvious

• But, the category of Stable is defined as a Failure
  • A patient with a Clinical Response but with < 25% radiologic improvement is scored as Failure-Stable

• This usually works for pulmonary IFD (especially IA)
  • But, extrapulmonary IFD can take months to respond
  • And even pulmonary IFD can sometimes be slow
  • Stable is the key prelude to Success: it enables further chemotherapy, transplantation, etc.

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1. IA = Invasive Aspergillosis
Some invasive mould infections require lengthy therapy

- Olorofim Phase 2: Proven IFD\(^1\)
  - \(~75\%\) highly immunosuppressed\(^2\)
  - All with limited treatment options
  - Months of prior therapy in some

- Main phase duration: 84 days
  - Adequate for some, but not all
  - Extended dosing provided for infections that are responding but need more therapy for a complex or challenging infection

- Stable at Day 84
  - Has been a common finding
  - Has been the prelude to ultimate Success at end of therapy

- A case is instructive...

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1. Probable IA per EORTC-MSG 2008/2019 is also permitted.
2. Hematologic malignancy, Hematopoietic Stem Cell Transplant (HSCT), or Lung Transplant
Chest-wall *L. prolificans* infection

- Aug ’18: 49-year-old healthy woman, breast augmentation
- Oct ’18: *L. prolificans* infection of right-sided breast implant
  - Spread to adjacent cartilage, sternum, and 4th-6th ribs
  - Voriconazole, terbinafine, miltefosine, posaconazole, and anidulafungin serially and in combination along with repeated debridement, hyperbaric oxygen
  - The infection remained uncontrolled; fungal colonies seen in wound
- Olorofim monotherapy begun 29 Nov 18
  - Day 84: EORTC-MSG Clinical Response of Success-Partial but Overall Response of Failure-Stable because of lag in radiologic improvement
  - Gradual wound closure over 322 days of therapy
Conclusions

• Day 42 All-Cause mortality is but has limitations
• EORTC-MSG defined an Overall response endpoint\(^1\)
  • It works well at Day 42 or 84 for most pulmonary IFD
  • It does not work for extrapulmonary (& some lung) infections
  • Some infections take months to response radiologically
  • Staying alive to reach that point is a Success
• It is important that Stable be defined as a Success
  • Could argue that it “comes out in the wash” to continue to define Stable as Failure
  • But the inconsistency is inconsistent with clinical practice
    • Common problem: ~20-40% Stable-Failure rate in recent trials\(^2,3\)
    • Scoring as Failure sends the wrong message to clinicians & payors: Stable can include substantial clinical improvement and better quality of life
    • Other causes of death arise during the 6-18 months needed to cure some infections ... improved quality of life may be lost to the label of “Stable”