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REVIEW PAPER

Mucormycosis (Black Fungs): A Review

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ABSTRACT

Mucormycosis is an angio invasive infection that occurs due to the fungi mucorales. It is a rare disease but increasingly recognized immune compromised patients. It can be categorized into rhino-orbito cerebral, cutaneous, disseminated, and pulmonary type. Overall increased mortality rate is reported, even though the aggressive treatment is given. The main aim and purpose of this project related to overview and treatment, prevention, drug profile and recent advanced in diagnostic and treatment method.

Keywords: - *Rhinocerebral, Mucormycosis, Fungal invasion.*

INTRODUCTION

Mucormycosis is very serious but rare fungal infection caused by a group of molds known as Mucormycetes [1]. These molds live throughout the environment. Mucormycetes mainly affect people who have health problem or take medicines that lower the body ability to fight germs and sickness[2]. It most commonly affects the sinuses or the lung after inhaling fungal spores from the air. It can also occur on the skin after a cut, burn, or other type of skin injury[3].

Types of Mucormycosis

1. Rhino-orbito-cerebral Mucormycosis

Rhino-orbito-cerebral mucormycosis of the order Mucorales. In this, there are a few subgroups like Rhizopes, Mucor, and Rhizomucor which are most commonly involved in this infection. These fungi are angioinvasive i.e., they invade the surrounding blood vessel and destroy them resulting in tissue necrosis and death.These molds line throughout environment and their spores are present in the air. They get lodged in the nasal cavity and adjoining sinuses. On reaching favorable milieu they ensconce themselves with in the tissue [6,7]. The spores germinate hyphae outgrow and release destructive juices which digest the host tissue and provide nutrition to the rapidly growing fungi.

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As they grow in nasal cavity they destroy the surrounding host tissue. The born in the nasal cavity & sinuses are destroyed. The masses may be seen in the nasal cavity and oral cavity. If it destroy the orbit and enters the eye socket it may cause bulging of the eye, pain, frozen eye movement and blindness.Once it enter the cranial cavity by breaching the skull base it blocks major arteries and venous lake resulting in major life –threating brain strokes and bleeds.The spores can some time travel into the depths of the respiratory system & get comfortably lodged in the lung parenchyma (alveoli & bronchioles) there the fungi grow rapidly, destroying the lung tissues compromising blood oxygenation. From there it can spread into the circulatory system resulting in an existential crisis.It mainly affects Nose, Eye & Brain [13].

Symptoms

- Black Spots on Nose
- Eye Pain
- Body Chills
- Headache
- Blur Vision
- Nasal Congestion

2. Pulmonary Mucormycosis

Pulmonary (lung) Mucormycosis is the most common type of Mucormycosis in people with cancer and in people who have had an organ transplant or a stem cell transplant. It mostly affects Lungs & Respiratory System [11].

Symptoms

- Fever
- Cough
- Chest Pain
- Shortens of Breath

3. Gastrointestinal Mucormycosis

Gastrointestinal Mucormycosis is more common among young children than adults, especially premature and low birth weight infants less than 1 month of age, who have had antibiotics, surgery, or medication that lower the body ability to fight germs and sickness.

4. Cutaneous (skin) Mucormycosis

Cutaneous after the fungi enter the body through a break in the skin (for example, after surgery, a burn or other type of skin trauma). This is the most common form of Mucormycosis among people who do not have weakened immune system [17].

5. Disseminated Mucormycosis

Disseminated Mucormycosis occur when infection spreads through the bloodstream to affect another part of the body. The infection most commonly affects the brain, but also can affect other organ such as the spleen, heart, and skin.

Antifungal Agents for the Treatment of Black Fungus:

Only amphotericin B (AMB) and its lipid formulations, and recently isavuconazole have been studied as first-line therapy for Mucormycosis. On the contrary, posaconazole has been mainly studied as salvage therapy. [9] The efficacy of these agents is based on limited clinical data and on preclinical in vitro/in vivo data, showing activity against Mucorales. It should be underlined though, that no validated minimum inhibitory concentration (MIC) breakpoints exist for any of these agents.

1. Lipid Formulations of Amphotericin B:

AMB is considered the drug of choice for primary treatment of Mucormycosis. The efficacy of AMB has been shown in both laboratory (in vitro and in vivo) and clinical studies. Although interpretive breakpoints to AMB have not been determined, high in vitro MICs to AMB have been observed in clinical isolates of Cunninghamella species. However, in a small study of non-Aspergillus invasive mould infections, an MIC for amphotericin B of ≤0.5 µg/mL was significantly associated with better 6-week outcomes. Lipid formulations of amphotericin B (liposomal AMB, LAMB; and AMB lipid complex, ABLC) have better therapeutic index than the conventional amphotericin B deoxycholate and are considered as the first-line therapy of Mucormycosis. As with many antifungal agents and mycoses, the optimal dosage for AMB and its formulations against Mucormycosis is still undetermined. The standard daily dose of LAMB and ABLC suggested by current guidelines is 5 mg/kg/day.[7,17] The in vitro activity of AMB against Mucorales is highly variable. Recently, researchers reported that among 524 clinical Mucorales isolates, the epidemiologic cut-off values (ECVs) ≥97.5% for amphotericin B were rather high: 2 µg/mL for L. corymbifera, 2 µg/mL for M. circinelloides, 4 µg/mL for R. arrhizus, and 2 µg/mL for R. microspores. These relatively high AMB MIC values support the use of higher daily dose of AMB to achieve clearance of Mucorales from tissues. Indeed, in a neutropenic murine model of pulmonary Mucormycosis, the efficacy of liposomal AMB was dose-dependent: a dose of 10 mg/kg/day has been proved to be more effective in reducing fungal burden compared to 5 or 1 mg/kg/day. Based on these in vitro and in vivo data, researchers proposed to treat Mucormycosis with high dose LAMB (>5 mg/kg/day). Yet, this recommendation has not been supported by the findings of a subsequent clinical study. The French Mycoses Study Group conducted a phase I–II prospective, multicenter, pilot trial on the efficacy and safety of high-dose (10 mg/kg/day) LAMB monotherapy (AmBizygo study) for the treatment of Mucormycosis. [17] The study included 40 patients, the majority of them with underlying hematological malignancy and/or HSCT. Surgery and debridement has been performed in 71% of the patients before initiation of

antifungal therapy. Compared to historical controls receiving the standard dose of 5 mg/kg/day, no improvements in mortality and response rates (38 and 36% respectively) was seen at 12 weeks of treatment. On the other hand, high dose L-AMB was associated with increased nephrotoxicity and electrolyte derangements. Characteristically, doubling of the baseline serum creatinine levels has been observed in 40% of the patients, dictating dose reduction. Although dosages beyond 5 mg/kg/day have not been proved to be more efficacious for Mucormycosis, they may be considered on an individual basis, especially when there is CNS or osteoarticular involvement

2. New Triazoles:

Act by depleting ergosterol from the fungal cell membrane. Among triazole antifungals, fluconazole, itraconazole, and voriconazole have little or no activity against Mucorales. Newer triazoles, namely posaconazole and isavuconazole, have better in vitro activity against Mucorales and clinical data supporting their use in Mucormycosis.[14]

Posaconazole:

Posaconazole has variable in vitro activity against Mucorales, which is species-dependent. A study of 131 clinical isolates showed that the median MICs of posaconazole for various Mucorales species varied widely between 1.0 and 8.0 µg/mL. In laboratory animal studies, experimental infections produced by Mucor spp. were most responsive to posaconazole, while those caused by Rhizopus spp. were usually non-responsive. Lewis et al. have shown in an immunosuppressed murine model of pulmonary Mucormycosis,that a posaconazole serum concentration higher than 4000 µg/mL is needed to suppress the growth of Rhizopusspp. with an MIC of 2 µg/mL. These data raise concerns on the clinical efficacy of posaconazole, at least in the current standard J. Fungi 2018, 4, 90 5 of 17 dose of 300 mg/day of extended release tablets, as Rhizopus is among the most common agents causing Mucormycosis. Clinical studies on the efficacy of posaconazole for Mucormycosis are scarce.[10] Early case reports and case series reported that posaconazole could be an option as salvage therapy in patients unresponsive or intolerant to LAMB. In a subsequent open-label trial including 24 patients, the success rate of salvage therapy with posaconazole oral suspension (800 mg in 4 divided doses) was 70%. The drug was well-tolerated with only minor gastrointestinal side-effects. In another retrospective study of posaconazole oral suspension as salvage therapy in 91 patients with refractory Mucormycosis, the response rate was 61%, and in the subgroup of patients with the pulmonary form of Mucormycosis 65%. An additional 21% of subjects had stable disease at the end of 12 weeks of treatment. Until recently, posaconazole was available only as oral suspension, administered three or four times daily, with food (preferably a high-fat meal) or with an acidic carbonated beverage, in order to enhance bioavailability. [12]

These food requirements make difficult the use of the oral solution in critically ill patients, as they might not be able to eat or they might be nauseous. Therefore, absorption of posaconazole oral suspension was often suboptimal leading to therapeutic failures. To overcome the pharmacokinetic limitations of the oral solution a gastro-resistant tablet and an intravenous (IV) solution has been developed. The advantages of the tablet formulation over the suspension include better bioavailability allowing once-daily dosage, no food requirements, and absorption unaffected by changes in gastric pH or motility; less interpatient variability and more predictable plasma concentrations than the suspension. Despite improved pharmacokinetics, therapeutic drug monitoring (TDM) is suggested for the tablets as it is the case for the suspension formulation.

Isavuconazole:

Isavuconazole is a new broad-spectrum triazole and is the biologically active agent of the prodrug isavuconazonium sulfate. It is approved in the United States for the treatment of Mucormycosis, and in Europe for the treatment of Mucormycosis when amphotericin B is not feasible. It is available in both intravenous and oral formulations and it is administered with a loading dose of 200 mg three times a day for two days and 200 mg daily thereafter. Isavuconazole has many pharmacokinetic and safety advantages compared to other azoles, including linear pharmacokinetics and thus no need for TDM; less drug–drug interactions; less toxicity, especially hepatotoxicity, skin and ocular side-effects, or QT prolongation; no nephrotoxic cyclodextrin in the IV formulation; no need for dose adjustment in kidney, liver failure or obesity; and excellent oral bioavailability with no food requirements.[16]

Amphotericin B

Amphotericin B injection is an antifungal used to treat fungal infection in HIV patients, neutropenic patients, cryptococcal meningitis, fungal infection and leishmaniasis.

Routes of Administration

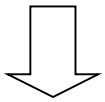
- Slow I.V for systemic fungal disease.
- Intrathecal for fungal C.N.S infection.
- Topical drops and direct subconjuctival injection for Mycotic corneal ulcer and keratitis.
- Local injection into the joint in fungal arthritis.
- Bladder irrigation in candiduria.

Mechanism of action

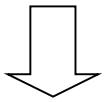
Amphotericin B is fungi static or fungicidal depending on the concentration obtained in body fluid and the susceptibility of the fungus.The drug acts by binding to sterols (ergo sterol) in the cell membrane of susceptible fungi. This creates a Trans membrane channel and the resultant change in membrane permeability allowing leakage of intracellular components.Ergo sterol, the principal sterol in the fungal cytoplasmic membrane, is the target site of action of Amphotericin B and the azoles.

Amphotericin B, polygene, binds irreversibly to ergo sterol, resulting in disruption of membrane integrity and ultimately cell death.[19]

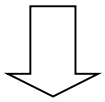
Amphotericin B



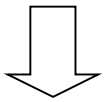
Binds ergo sterol in fungal cell membrane



From pores in cell membrane



Cell contents leak out



Cell death

CONCLUSION

To conclude, Mucormycosis is a disease which usually show aggressive and an alarming mortality rate. However the actual etiopathogenesis remains varied throughout the world, diagnosis of this disease remains a challenge for the clinicians. But still in the view of its high mortality rate,

- Early and promote diagnosis
- Recovery from the predisposing factors
- Early intervention with surgical debridement and therapeutic drugs are the only hopes to improve the condition from this devasting disease.

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