Cerebral Rhizomucor Infection Treated by Posaconazole Delayed-Release Tablets in an Allogeneic Stem Cell Transplant Recipient

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Abstract
Mucormycosis (zygomycosis) is an emerging fungal disease in allogeneic hematopoietic stem cell transplant (allo-HSCT) recipients. A 30-year-old woman diagnosed with acute myelomonocytic leukemia and needing allo-HSCT presented pulmonary and cerebral infection due to Rhizomucor pusillus. This fungal infection was treated with surgical treatment and posaconazole delayed-release tablets. This strategy allowed reaching high drug levels that could not be obtained with the posaconazole solution.

Reference

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Case Report

Cerebral Rhizomucor Infection Treated by Posaconazole Delayed-Release Tablets in an Allogeneic Stem Cell Transplant Recipient

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1. Introduction

Rhizomucor is an emerging fungal pathogen in allogeneic hematopoietic stem cell transplant (allo-HSCT) recipients belonging to the group of Zygomycetes. Its incidence is rising in the context of wide voriconazole use. Cerebral Rhizomucor infection is associated with especially high mortality and treatment must combine aggressive surgical debridement, antifungal therapy and restoration of immune function whenever possible. Recently posaconazole delayed-release tablets, registered for antifungal prophylaxis, have allowed yielding higher plasma levels than the conventional posaconazole oral solution. Nevertheless the role of posaconazole new formulations remains to be defined in therapeutic indications. Here we describe the case of a cerebral Rhizomucor infection successfully treated by posaconazole delayed-release tablets in an allo-HSCT recipient.

2. Case report

A 30-year-old Brazilian woman diagnosed with acute myelomonocytic leukemia underwent cytarabine-based chemotherapy. At admission she presented with several pulmonary nodular lesions on CT-scan, suggestive of fungal origin. The initial treatment consisted in empirical voriconazole (Vfend, Pfizer) 200 mg every 12 hours i.v. during three weeks. Due to radiological progression despite antifungal therapy she underwent a surgical resection consisting in a right inferior lobectomy and wedge resections of two left superior lobe nodules. Microbiological analysis of the nodules revealed positive direct examination for mycelium elements identified as Rhizomucor pusillus by 18S panfungal qPCR followed by sequence-based identification (GenBank accession number HQ845298.1), whereas culture remained negative. Liposomal amphotericin-B (AmBisome, Gilead Sciences) at 5 mg/kg/day followed by posaconazole oral suspension (Noxafl, MSD) 400 mg every 6 hours, were administered for six months and subsequently stopped due to remission.

Nineteen months after the initial diagnosis leukemia relapsed and the patient underwent FLAG (fludarabine, idarubicine, cytarabine, granulocyte colony stimulating factor (G-CSF)) chemotherapy. At admission a new pulmonary excavated lesion was seen in the left superior lobe (at the sites of prior

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wedge resections). A left superior lobectomy was performed. Pathological and microbiological examinations, as well as panfungal PCR (fungal inter spacer region (ITS) conventional PCR) remained negative.\(^8\) Suspecting a relapse of the \textit{Rhizomucor} infection, liposomal amphotericin-B was restarted at 5 mg/kg/day. The patient remained in aplasia, and allogeneic hematopoietic stem cell transplantation (allo-HSCT) was considered the only life saving option. In the pre-transplantation workup performed under meropenem and liposomal amphotericin-B treatment, three cerebral nodules were found in the right middle temporal gyrus, the right frontal inferior gyrus and the right frontal inferior gyrus on cerebral MRI, motivating addition of posaconazole suspension. CSF cultures and panfungal PCR, blood cultures, as well as blood galactomannanes remained negative. After two inconclusive cerebral biopsy attempts, a blood cultures, as well as blood galactomannanes remained negative.8 Suspecting a relapse of the panfungal PCR (fungal inter spacer region (ITS) conventional PCR) remained negative.\(^8\) Suspecting a relapse of the infection, liposomal amphotericin-B was restarted at 5 mg/kg/day. The patient remained in aplasia, and allogeneic hematopoietic stem cell transplantation (allo-HSCT) was considered the only life saving option. In the pre-transplantation workup performed under meropenem and liposomal amphotericin-B treatment, three cerebral nodules were found in the right middle temporal gyrus, the right frontal inferior gyrus and the right frontal inferior gyrus on cerebral MRI, motivating addition of posaconazole suspension. CSF cultures and panfungal PCR, blood cultures, as well as blood galactomannanes remained negative. After two inconclusive cerebral biopsy attempts, a blood cultures, as well as blood galactomannanes remained negative.8 Suspecting a relapse of the infection, liposomal amphotericin-B was restarted at 5 mg/kg/day. The patient remained in aplasia, and allogeneic hematopoietic stem cell transplantation (allo-HSCT) was considered the only life saving option. In the pre-transplantation workup performed under meropenem and liposomal amphotericin-B treatment, three cerebral nodules were found in the right middle temporal gyrus, the right frontal inferior gyrus and the right frontal inferior gyrus on cerebral MRI, motivating addition of posaconazole suspension. CSF cultures and panfungal PCR, blood cultures, as well as blood galactomannanes remained negative. After two inconclusive cerebral biopsy attempts, a blood cultures, as well as blood galactomannanes remained negative.8 Suspecting a relapse of the infection, liposomal amphotericin-B was restarted at 5 mg/kg/day. The patient remained in aplasia, and allogeneic hematopoietic stem cell transplantation (allo-HSCT) was considered the only life saving option. In the pre-transplantation workup performed under meropenem and liposomal amphotericin-B treatment, three cerebral nodules were found in the right middle temporal gyrus, the right frontal inferior gyrus and the right frontal inferior gyrus on cerebral MRI, motivating addition of posaconazole suspension. CSF cultures and panfungal PCR, blood cultures, as well as blood galactomannanes remained negative. After two inconclusive cerebral biopsy attempts, a blood cultures, as well as blood galactomannanes remained negative.8

\[ \text{Fig. 1. Direct examination (Fungifluor) of mycelium elements, with large septations and absence of branches highly suggestive in the context of Rhizomucor.} \]

3. Discussion

In hematological malignancies and bone marrow transplant patients, lung and rhino-cerebral are the most common sites of \textit{Rhizomucor} infection. CNS abscesses infections are not rare; in a large published series of mucormycosis (zygomycosis), 283 cases involved the brain.\(^2\) These infections are severe, of rising importance and incidence probably in the context of wide voriconazole use for both treatment of invasive aspergillosis or for secondary prophylaxis. Cerebral mucormycosis is associated with a high mortality rate of 50%.\(^3\)

Cerebral fungal infections, and especially cerebral mucormycosis, remain difficult to treat because of the poor CNS penetration of most antifungals, as well as the absence of activity against Zygomycetes of most antifungals, including fluconazole, voriconazole and echinocandins. Cure is rarely achieved without surgical removal.

Itraconazole, posaconazole and the newly FDA-approved isavuconazole have activity against Zygomycetes. In salvage therapies, posaconazole, which has moderate CNS penetration appeared as a cornerstone for treatment of (cerebral) mucormycosis with a response rate of >60%.\(^9\)–\(^12\) Although no exact therapeutic guidelines exist for cerebral mucormycosis, posaconazole solution is recommended for salvage therapy at a posology of 800 mg/day in addition to high dose liposomal amphotericin-B.\(^11\) However achieving adequate posaconazole serum levels has been challenging with the oral solution. In this setting, posaconazole delayed-released tablets, achieving higher serum levels than the oral solution are a promising option.

Here we describe a case of a cerebral \textit{Rhizomucor} infection in an allo-HSCT recipient treated successfully with an antifungal regimen containing posaconazole delayed-release tablets and liposomal amphotericin B, combined to surgery. It is to our knowledge the first description of such therapeutic option in cerebral mucormycosis. Posaconazole delayed-release tablets allowed to reach therapeutic drug levels > 2 mg/L that could not be obtained with the standard solution.

Few information are available for posaconazole delayed-release tablets, Phase I studies showed >97% reaching therapeutic levels with 300 mg once daily in PK/PD studies.\(^14\)\(^15\)

No published clinical trials are available on efficacy of posaconazole delayed-release tablets in the prevention of IFIs in immunocompromised patients, although it seems probable that achieving higher blood posaconazole level will confer at least as good protection against IFI than the suspension. The place of posaconazole delayed tablets for IFI treatment needs to be defined as no clinical trials are available. So far there is only a single report on a case of a 65-year-old man with an \textit{Aspergillus} brain abscess, treated with surgical resection and voriconazole for one year, and subsequently treated with posaconazole delayed-release tablets at 300 mg/day efficiently and safely.\(^16\)

Our observation suggests that posaconazole delayed-release tablets are an interesting therapeutic option for cerebral mucormycosis, due to the higher drug levels obtained. These might even be increased with the more recently FDA-approved intravenous posaconazole formulation. Clinical trials with these new posaconazole formulations are needed and will hopefully show an increase of successful response to treatment and survival.

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