Medical Mycology Case Reports 11 (2016) 36–39

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

Isavuconazole as salvage therapy for mucormycosis

Bianca Graves [a,*], C. Orla Morrissey [a,b], Andrew Wei [c], John Coutsouvelis [d,e], Samantha Ellis [f], Alan Pham [g], Julian Gooi [h], Michelle Ananda-Rajah [i]

[a] Department of Infectious Diseases, Alfred Hospital, Melbourne, Australia
[b] Department of Infectious Diseases, Monash University, Melbourne, Australia
[c] Department of Haematology, Alfred Hospital, Melbourne, Australia
[d] Department of Pharmacy, Alfred Hospital, Melbourne, Australia
[e] Centre for Medication Usage and Safety, Monash University, Melbourne, Australia
[f] Department of Radiology, Alfred Hospital, Melbourne, Australia
[g] Department of Anatomical Pathology, Alfred Hospital, Melbourne Australia
[h] Department of Cardiothoracics, Alfred Hospital, Melbourne, Australia
[i] General Medical Unit, Alfred Hospital, Melbourne, Australia

ARTICLE INFO

Article history:
Received 30 December 2015
Received in revised form
2 March 2016
Accepted 7 March 2016
Available online 8 March 2016

Keywords:
Mucormycosis
Isavuconazole

ABSTRACT

Mucormycosis carries a high mortality rate with few therapeutic options available. We describe a man with pulmonary/splenic mucormycosis complicating hypoplastic myelodysplastic syndrome on a background of chronic kidney disease, who achieved a complete response with salvage isavuconazole therapy following intolerance of consecutive courses of liposomal amphotericin and posaconazole therapy.

1. Introduction

Mucormycosis, an infection caused by fungi of the order Mucorales, typically presents as an aggressive angio-invasive disease in immunosuppressed hosts. Patients with hematological malignancies and recipients of hematopoietic stem cell transplants are at highest risk for pulmonary mucormycosis with reported mortality rates of up to 76% [1].

Early diagnosis and aggressive management with surgical debridement and antifungal treatment are critical for optimal outcomes [2]. Previously, the only two systemic antifungals available with reliable activity against Mucorales were amphotericin B and posaconazole. Isavuconazole, a new extended-spectrum triazole with activity against yeasts, molds and dimorphic fungi, has recently been approved for treatment of invasive aspergillosis and mucormycosis [3]. We report a case of successful salvage treatment of pulmonary/splenic mucormycosis with isavuconazole, in a hematology patient intolerant of primary therapy with liposomal amphotericin B and posaconazole.

2. Case

A 59 year old male gardener was transferred from another hospital with left lower lobe pneumonia unresponsive to nine days of intravenous broad-spectrum antibiotics. This was on a background of a recent diagnosis of hypoplastic myelodysplastic syndrome (MDS). His hypoplastic MDS had been treated, 38 days earlier, with antithymocyte globulin (ATG) and five days of pulsed intravenous methylprednisolone (1 mg/kg/day). At presentation, he was taking cyclosporine 200 mg orally twice daily and a tapering dose of prednisolone, 5 mg daily. His neutrophil count was 1.1 cells/mm^3 at presentation, however in the six weeks prior, had been < 1.0 cells/mm^3. Antifungal prophylaxis with posaconazole oral solution, 200 mg three times daily (TDS), had been commenced at the onset of ATG and methylprednisolone treatment. This was increased to 200 mg four times daily (QID), following a sub-therapeutic serum concentration of 0.3 μg/ml, seven days after commencement.

His past medical history was significant for chronic kidney disease due to primary focal and segmental hyalinosis and sclerosis, presenting as nephrotic syndrome in 2012, resulting in chronic proteinuria and a baseline creatinine clearance 91 ml/min.

At presentation to our institution, chest computed tomography (CT) (Fig. 1A) revealed a cavitating left lower lobe lesion with contiguous splenic involvement, suspicious for invasive fungal disease (IFD). Sinus imaging was clear. Empirical treatment was commenced with liposomal amphotericin B (L-AmB) 5 mg/kg and piperacillin-tazobactam 4.5 mg QID. Histopathology on a CT guided biopsy, obtained on day 2 of admission, demonstrated broad

* Corresponding author.

http://dx.doi.org/10.1016/j.mmcr.2016.03.002

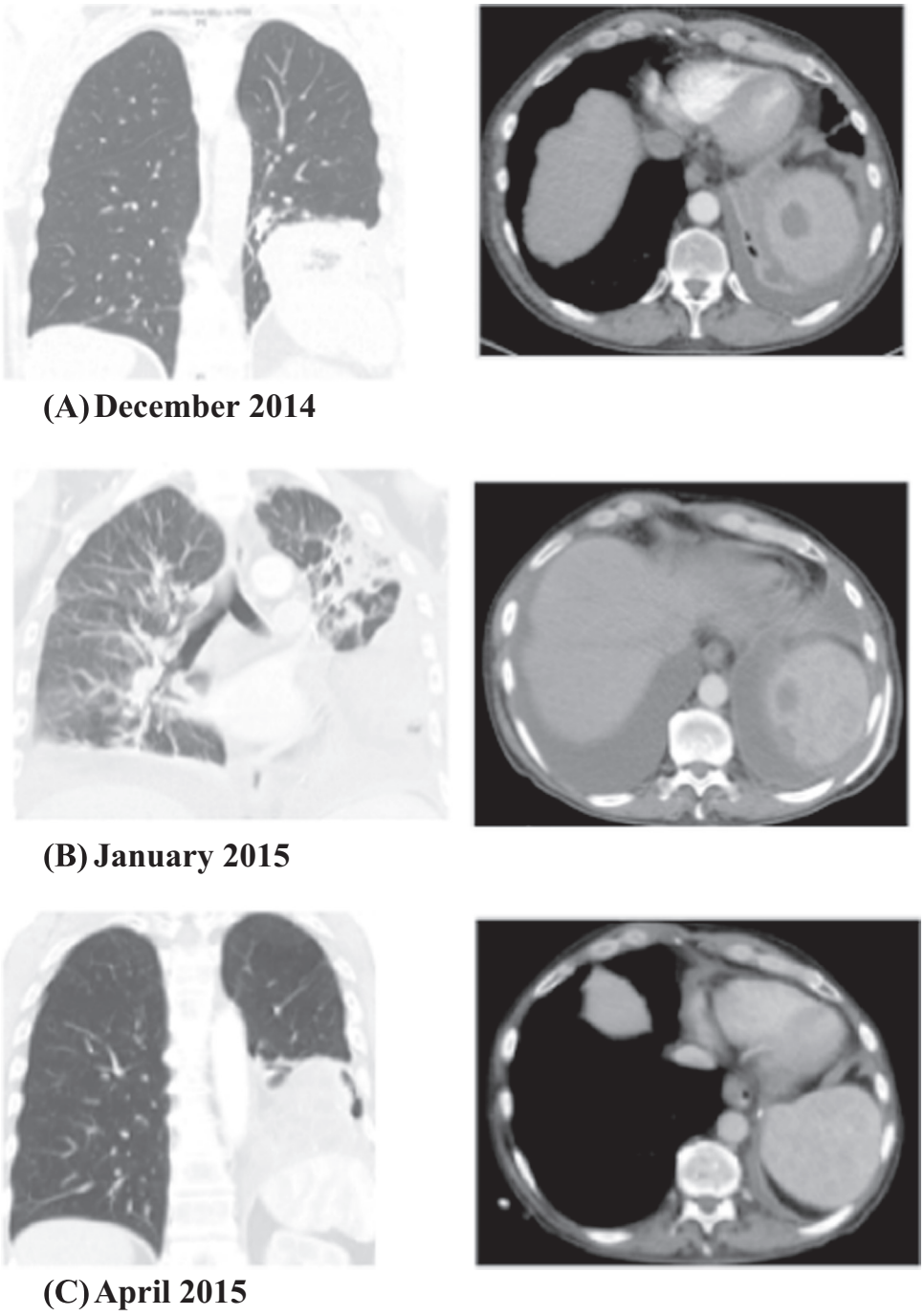

Fig. 1. (A) CT chest at diagnosis demonstrating right lower lobe lesion with "reverse halo sign" and contiguous splenic involvement. (B) CT Chest following clinical deterioration post lobectomy demonstrating bilateral pleural effusions and peri-bronchial consolidation with a second splenic lesion. (C) CT Chest 11 weeks post isavuconazole therapy demonstrating resolution of the splenic lesions. Abbreviations: CT = computed tomography.

ribbon-like hyphae within necrotic tissue (Fig. 2), consistent with mucormycosis. On day 4 of admission he underwent a left lower lobectomy, with latissimus dorsi muscle flap transposition. Culture and pan-fungal PCR were negative, on both CT-guided biopsy and resected lung tissue.

The patient deteriorated clinically 15 days post lobectomy (Day 19 of L-AmB therapy) with hypoxia, delirium, renal failure and raised inflammatory markers. Repeat chest CT demonstrated bilateral pleural effusions with significant peri-bronchial consolidation in the remaining left lung and evidence of a new subcapsular splenic lesion concerning for disease progression (Fig. 1B). A right-sided pleurocentesis revealed a transudate and was culture negative. The patient was re-commenced on pipercillin-tazobactam and underwent diuresis. Posaconazole oral solution, 300 mg TDS, was added to L-AmB 5 mg/kg and increased to 300 mg QID following a sub-therapeutic level of 0.38 μg/ml, six days after commencement.

The patient achieved clinical stability on day 21, but was intolerant of high-dose posaconazole with severe nausea unresponsive to multiple anti-emetics, requiring a dose reduction to 200 mg TDS. Worsening renal function, with a reduction in creatinine clearance to 30 ml/min, after 46 days of L-AmB and despite ceasing cyclosporine and other nephrotoxic medications, prompted consideration of isavuconazole.

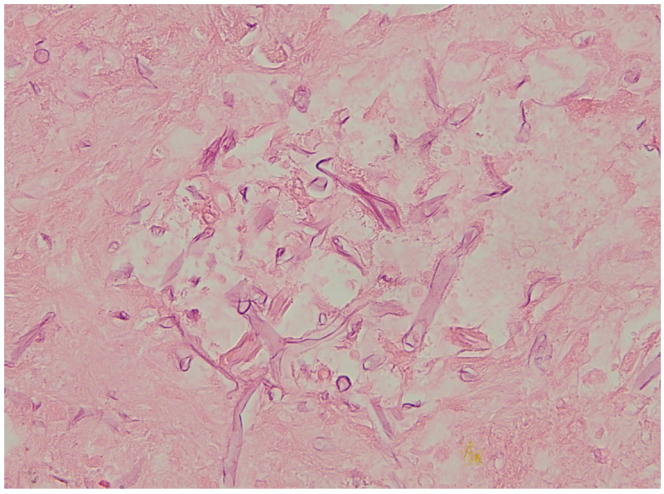

Fig. 2. Histopathology of excised lung showing broad ribbon-like hyphae within necrotic tissue, consistent with mucormycosis (H&E $\times 40$).

Sample ID	Analyte	Conc [ng/mL]
Day 3, pre-dose	BAL4815	2520
Day 3, pre-dose	BAL4815	2540
Day 5, pre-dose	BAL4815	2540
Day 5, pre-dose	BAL4815	2580
Day 7, pre-dose	BAL4815	2550
Day 7, pre-dose	BAL4815	2490
Day 7, 2 hours post	BAL4815	4800
Day 7, 2 hours post	BAL4815	4760
Day 7, 4 hours post	BAL4815	3580
Day 7, 4 hours post	BAL4815	3520
Day 7, 8 hours post	BAL4815	2990
Day 7, 8 hours post	BAL4815	3140

Fig. 3. Isavuconazole levels (measured at pre-specified time intervals; as per manufacturer's instructions).

Isavuconazole was obtained on compassionate access and commenced on day 48 post lobectomy (Day 52 of L-Amb) according to the manufacturer's instructions, with a loading dose of 200 mg intravenously TDS for 2 days. The patient received a further four days of intravenous therapy 200 mg daily, before changing to oral therapy, also at a dose of 200 mg daily. Serum concentrations of isavuconazole were monitored at regular intervals according to the manufacturer's protocol (Fig. 3) and were considered to be within therapeutic range.

The patient was discharged day 50 following lobectomy and six days after commencing isavuconazole. While on isavuconazole 200 mg orally daily, he continued to experience Grade 1 nausea, requiring three anti-emetic agents, which was marginally improved relative to posaconazole therapy. There was no derangement of his liver function tests throughout therapy. His renal function improved to his baseline creatinine clearance of >90 ml/min. Serial imaging after 102 days of isavuconazole therapy (Fig. 1C) showed complete resolution of the splenic lesions and treatment was ceased.

3. Discussion

To the best of our knowledge, this is the first report of the use of isavuconazole in Australia. Isavuconazole is a broad-spectrum triazole pro-drug, which is licensed for primary and salvage treatment of mucormycosis. A sub-group of 37 patients with proven/probable mucormycosis in a phase 3, open-label, non-comparator trial (VITAL) [4] achieved response rates of 31.6% for primary therapy and 36.4% for salvage therapy [5,3].

The mainstay of management of mucormycosis has, until recently, been polyene antifungal therapy and surgical debridement [2]. Amphotericin B has reported response rates of 31–39% [6] and L-AmB is recommended as first line therapy [2]. In our case, empirical L-AmB was delayed by nine days with delays in treatment of mucormycosis beyond three days associated with an increased mortality [7,8]. Despite this, our patient recovered with aggressive surgical debridement and multiple antifungal agents including salvage isavuconazole therapy. Posaconazole and L-AmB had to be prematurely ceased due to gastrointestinal side-effects and nephrotoxicity, respectively.

Until recently, posaconazole and amphotericin B based formulations have been the only antifungal agents with reliable activity against the Mucorales species. Posaconazole has shown response rates of up to 60% as salvage therapy for mucormycosis, however erratic bioavailability of the oral solution has limited its use [9]. Posaconazole serum levels in our patient remained subtherapeutic despite dose escalation up to 1200 mg daily, resulting in severe nausea. Severe nausea has been reported elsewhere with dose-escalation beyond recommended the dosages [10].

The favorable physico-chemical and toxicity profile of isavuconazole contributed to our patient's successful outcome. Isavuconazole has excellent oral bioavailability, a predictable pharmacokinetic profile and the absence of a solubilizing agent such as cyclodextrin, obviates concerns of nephrotoxicity in patients with underlying kidney disease [5]. It has few reported significant adverse effects [5] and, other than nausea, was relatively well tolerated by our patient over prolonged treatment course lasting 102 days. Similar tolerability was evident among the 5 patients from VITAL study who had complete response with treatment courses lasting 179, 180 and 509 days, respectively for primary treatment and 86 and 735 days, respectively for disease refractory to other systemic antifungal therapy [9,3]. Case reports have documented complete response of disseminated and sino-orbital mucormycosis with prolonged salvage therapy with isavuconazole lasting 29 weeks and 16 months days, respectively [11,12].

Our case demonstrates a role for isavuconazole for treatment of mucormycosis when therapeutic options are limited due either to renal impairment or dose-limiting toxicities of other antifungal agents.

Conflict of interest

COM has been on the advisory board for, received investigator-initiated grants from and given lectures for Gilead Sciences, Merck

Sharp and Dohme and Pfizer. All honoraria have been paid directly to Alfred Hospital.

Acknowledgments

None.

References

[1] G. Petrikkos, A. Skiada, O. Lortholary, T. Walsh, Kontoyiannis, Epidemiology and clinical manifestations of mucormycosis, Clin. Infect. Dis. 54 (Supp. 1) (2012) S23–S34.
[2] A. Skiada, F. Lanternier, A.H. Groll, L. Pagano, S. Zimmerli, R. Herbrecht, O. Lortholary, G.I. Petrikkos, Diagnosis and treatment of mucormycosis in patients with haematological malignancies: guidelines from the 3rd European Conference on Infections in Leukaemia (ECIL 3), Haeamtologica 98 (4) (2013), pp. 492–504.
[3] Astellas: FDA Advisory Committee Briefing Document: Isavuconium – Invasive Aspergillosis and Invasive Mucormycosis. ⟨www.fda.gov/downloads⟩.
[4] F.M. Marty, J.R. Perfect, O.A. Cornely, et al., An open-label Phase 3 study of isavuconazole (VITAL): focus on mucormycosis. Presented at: ID week ASM. PA, USA 8–12 October 2014 (Abstract no. 824).
[5] M. Ananda-Rajah, D. Kontoyiannis, Isavuconazole: a new extended spectrum triazole for invasive mould infections, Future Microbiol. 10 (5) (2015) 693–708.
[6] M. Roden, T. Zaoutis, W. Buchanan, et al., Epidemiology and outcome of zygomycosis: a review of 929 reported cases, Clin. Infect. Dis. 47 (2008) 503–509.
[7] G. Chamilos, R.E. Lewis, D.P. Kontoyiannis, Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with haematological malignancy who have zygomycosis, Clin. Infect. Dis. 47 (4) (2008) 503–509.
[8] T. Walsh, M. Gamaletsou, M. McGinnis, R. Hayden, D. Kotoyiannis, Early clinical and laboratory diagnosis of invasive pulmonary, extrapulmonary, and disseminated mucormycosis (zygomycosis), Clin. Infect. Dis. 54 (Supp. 1) (2012) S55–S60.
[9] O. Cornley, J. Vehreschild, M. Ruping, Current experience in treating invasive zygomycosis with posaconazole, Clin. Microbiol. Infect. 15 (2009) S77–S81.
[10] R. Shields, C. Clancy, Vadnerkar, E. Kwak, F. Silveira, et al., Posaconazole serum concentrations among cardiothoracic transplant recipients: factors impacting trough levels and correlation with clinical response to therapy, Antimicrob. Agents Chemother. 55 (3) (2011) 1308–1311.
[11] J. Ervens, M. Ghannoum, B. Graf, S. Schartz, Successful isavuconazole salvage therapy in a patient with invasive mucormycosis, Infection 42 (2014) 429–432.
[12] D. Peixoto, L. Gagne, Hammond, E. Gilmore, A. Joyce, R. Soiffer, F. Marty, Isavuconazole treatment of a patient with disseminated mucormycosis, J. Clin. Microbiol. 52 (3) (2014) 1016–1019.