





Case Report

Isavuconazole prophylaxis against invasive fungal infections in allogeneic stem cell transplantation: A single-center experience



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Introduction

Patients undergoing allogeneic stem cell transplantation (allo-HCT) require profound immunosuppression is required to preserve graft function and prevent graft-versus host disease (GVHD), resulting in a high risk of infectious complications such as invasive fungal diseases (IFIs). Posaconazole is approved for primary antifungal prophylaxis alloHCT. However, posaconazole is associated with drug-drug interactions which may lead to relevant toxicities limiting it uses in hematological patients. Other triazoles, amphotericin B, and echinocandins can be used in patients at high risk of IFIs. However, there is less evidence supporting the efficacy of these drugs for the prevention of IFIs.¹

Isavuconazole is a new generation triazole with broad-spectrum antifungal activity approved for the treatment of invasive aspergillosis (IA) and mucormycosis. In comparison with other azoles, isavuconazole has a favorable pharmacokinetics, superior tolerability, less associated toxicities and drug-drug interactions. The efficacy of isavuconazole as antifungal prophylaxis in immunocompromised patients is supported by publications.^{2–8} Nevertheless, its use as part of regular clinical practice is not standardized. We report a single center experience using isavuconazole for antifungal prophylaxis after alloHCT. Compassionate use of isavuconazole was obtained from our local Institutional Review Board, and the treatment was initiated in accordance with the principles of the Declaration of Helsinki.

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Cases presentation

Case 1: A 40-year-old female with ALK-positive anaplastic lymphoma received RIC alloHCT from a 10/10 HLA MRD after achieving third complete remission in February 2019. Disease relapse was diagnosed five months after alloHCT, and it was successfully treated with four cycles of brentuximab vedotin. Two donor lymphocyte infusions were administered as a consolidative approach. Overlapping severe chronic GVHD involving skin, oral mucosa, eyes and liver was diagnosed in April 2020. High dose prednisone, therapeutic tacrolimus, and extracorporeal photopheresis were started in combination with isavuconazole for antifungal prophylaxis. The patient presented clinical response to GVHD. No fungal infections, adverse events or drug–drug interactions with tacrolimus were documented. Isavuconazole prophylaxis was discontinued after 5 months, once prednisone was withdrawn.

Case 2: A 45-year-old male with acute myeloblastic leukemia in complete remission underwent a 10/10 HLA MRD, RIC alloHCT in February 2019. Severe ocular and lung cGVHD was diagnosed in November 2019 and treated with prednisone and sirolimus, followed by dasatinib. Severe COVID19 pulmonary infection was diagnosed April 2020, and it was resolved after hydroxychloroquine, a single dose of tocilizumab, and steroids. COVID19 disease triggered a flare of the cGVHD causing severe respiratory insufficiency in May 2020. Prednisone was increased to 2 mg/kg and sirolimus, and dasatinib were continued. Isavuconazole was started. Sirolimus dose has not required adjustment during the follow-up, and to date, the patient continues to be on isavuconazole prophylaxis. No fungal infections or adverse events have been documented.

Case 3: A 25-year-old female with Hodgkin lymphoma in partial remission after four lines of treatment underwent RIC alloHCT from a 10/10 HLA MRD in February 2019. GVHD prophylaxis was composed of PTCY-MMF and CsA. CsA was discontinued secondary to posterior reversible encephalopathy syndrome on day +18. Grade IV skin acute GVHD was diagnosed on March 2019. High-dose steroids and sirolimus were started, and primary antifungal prophylaxis with isavuconazole was added. Neither drug interactions nor fungal infections were documented during the 5 months that the patient was on isavuconazole prophylaxis. Complete response of the clinically relevant GVHD was achieved. Multiple infections and viral reactivations complicated the post-transplant phase leading into a poor graft function. The patient was admitted on July 2019 because of septic shock secondary to *E. coli* bloodstream infection. The course was complicated with a respiratory insufficiency due to alveolar hemorrhage and the patient deceased on August 2019.

Case 4: A 58-year-old female with diffuse large B-cell lymphoma in complete remission after three lines of treatment underwent RIC alloHCT from a haploidentical donor in July 2020. GVHD prophylaxis consisted of PTCY, MMF and tacrolimus. Acute cardiogenic pulmonary edema and severe kidney injury with an elevation of the creatinine levels up to 188 $\mu\text{mol/L}$ was diagnosed on day +10. GVHD prophylaxis was modified to methylprednisolone followed by sirolimus in monotherapy. Antifungal prophylaxis was modified to

isavuconazole, and no breakthrough fungal infections, drug interactions, or adverse events were diagnosed. Sirolimus dose did required adjustment after starting isavuconazole prophylaxis. Primary anti-fungal prophylaxis with isavuconazole was discontinued at day +100 after haploHCT as per protocol.

Case 5: A 64-year-old female with Philadelphia-negative acute lymphoblastic leukemia underwent RIC alloHCT from a 10/10 HLA MRD after achieving a second complete remission on December 2019. Pulmonary IA was diagnosed two months before alloHCT and was successfully treated with voriconazole 200 mg/12 h. Secondary prophylaxis with voriconazole was started after alloHCT with the aim of being continued until the discontinuation of the immunosuppression (tacrolimus). Rising liver and cholestatic enzymes were documented since the early post-transplant phase with a significant worsening on April 2020. Voriconazole was switched to isavuconazole on May 2020 and a progressive normalization of liver function tests was documented. Tacrolimus dosage did not required adjustment. Isavuconazole was continued for 8 weeks and no toxicities or IA recurrences were diagnosed.

Discussion

In summary, we report a single-center experience using isavuconazole for broad-spectrum antifungal prophylaxis after alloHCT. After starting isavuconazole prophylaxis there was not any suspicion of invasive fungal disease, and breakthrough IFIs and IA reactivations were not documented. No adverse events were diagnosed. Antifungal prophylaxis is a challenging aspect of the post-alloHCT care. The strong inhibition of CYP3A4 enzyme mediated by posaconazole and voriconazole can increase plasma concentrations of immunosuppressant drugs requiring a close and universal monitoring of pharmacological levels. Micafungin or amphotericin B can be used as an alternative to minimize pharmacological interactions; however, these drugs are administered intravenously.¹ Several aspects make isavuconazole a good candidate for antifungal prophylaxis in alloHCT, and its efficacy for IFIs prevention has been explored with promising results. Main studies supporting the effectiveness of isavuconazole used for antifungal prophylaxis on immunocompromised patients are summarized in Table 1.^{2–8} Although isavuconazole is a moderate CYP3A4 inhibitor and drug–drug interactions need to be taken into consideration, they seem to be modest in comparison with other triazoles.⁹ Our experience shows that tacrolimus and sirolimus dose did not had to be modified during the duration of isavuconazole prophylaxis. However, conclusions are limited by the reduced sample size. With some exceptions, plasmatic levels of isavuconazole do not need to be routinely monitored. In addition, it counts with an intravenous and oral disposition expanding the use of this drug for the inpatient and outpatient management. Isavuconazole induces less hepatobiliary toxicity than other triazoles, conferring an advantage for the use of this newly triazole in alloHCT.^{2–8} The safety of isavuconazole administration in patients with renal impairment has also been investigated with positive results.¹⁰

In summary, the use isavuconazole for prophylaxis against IFDs is not established. However, the reduced pharmacological

Table 1 – Isavuconazole prophylaxis against invasive fungal infections in allogeneic stem cell transplantation: A single-center experience.

	N	Population	Enrolling period	Study Design	Indication	Main results
Stern et al. ²	Total: 95	Adults HCT	2017–2018	Prospective Open-label single-arm study	Effectiveness of isavuconazole prophylaxis after HCT	Breakthrough candidemia rate was 3.1%. Absence of invasive mold infections. Drug-related toxicities leading to discontinuation: 7.4% (hepatotoxicity and rash)
Bose et al. ³	Total: 65	Adults AML/MDS	2017–2019	Prospective Phase 2 Trial	Effectiveness of isavuconazole prophylaxis in patients with AML and MDS	Probable/Proven Breakthrough IFIs: 6% and 8% respectively Excellent tolerability Drug-related toxicities 5% (mild/moderate hepatotoxicity) 0% QTc prolongations.
Fontana et al. ⁴	Total: 145	Adults Hematological Malignancies HCT	2016–2018	Retrospective Single-Centre Cohort Study	Effectiveness of isavuconazole prophylaxis	Breakthrough IFIs: 8.3% (all during neutropenia)
Decembrino et al. ⁵	Total: 29	Pediatric Hemato-Oncologic Malignancies HCT	2017–2018	Retrospective Multicenter Case Series	Effectiveness of isavuconazole as treatment or prophylaxis	IFIs overall response rate: 70.8% No breakthrough infections were registered Drug-related toxicities: 20% (hepatotoxicity) No drug-drug interactions with immunosuppressant
Hassouna et al. ⁶	Total: 91	Adults Hemato-Oncologic Malignancies Transplantation	2015–2017	Retrospective Single-Centre Cohort Study	Effectiveness of isavuconazole as treatment or prophylaxis	IFIs overall response rate: 62% No breakthrough infections were registered Drug-related toxicities: 0.1% (hepatotoxicity)
Bowen et al. ⁷	Total: 98	Adults Hemato-Oncologic Malignancies Transplantation	2015–2017	Retrospective Single-Centre Cohort Study	Clinical and economic outcomes associated with the use of isavuconazole as antifungal prophylaxis	Breakthrough infections: 8.5% Drug-related toxicities led to early discontinuation: 4.6% (hepatotoxicity) Switch to isavuconazole prophylaxis resulted in an estimated mean drug cost savings of \$128.25 per DOT relative to estimated posaconazole costs ($P < 0.001$).
Cornely et al. ⁸	Total: 20	Adults AML	2006–2007	Open-Label Dose Escalation Study	Safety and pharmacokinetics of intravenous isavuconazole prophylaxis	Treatment success: 90% Drug-related toxicities: 65% (headache and rash) Two patients discontinued the study due to adverse events.

interactions, less hepatobiliary induced toxicity in comparison to other triazoles, and its safety pattern in patients with renal impairment make it uses attractive for primary IFDs prophylaxis alloHCT.

Conflicts of interest

The authors declare no conflicts of interest.

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