Received: 16 January 2023 | Revised: 20 March 2023 | Accepted: 25 March 2023

DOI: 10.1111/bcp.15743

CASE REPORT

Clinically relevant bidirectional drug-drug interaction between midostaurin and voriconazole

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Funding information
This work was not funded.

Midostaurin is often prescribed with azole antifungals in patients with leukaemia, either for aspergillosis prophylaxis or treatment. Midostaurin is extensively metabolized by cytochrome (CYP) 3A4. In addition, it inhibits and induces various CYPs at therapeutic concentrations. Thus, midostaurin is associated with a high potential for drug-drug interactions (DDIs), both as a substrate (victim) and as a perpetrator. However, data on midostaurin as a perpetrator of DDIs are scarce, as most pharmacokinetic studies have focused on midostaurin as a victim drug. We report a clinically relevant bidirectional DDI between midostaurin and voriconazole during induction treatment. A 49-year-old woman with acute myeloid leukaemia developed invasive pulmonary aspergillosis after induction chemotherapy. She was treated with voriconazole at standard dosage. Six days after starting midostaurin, she developed visual hallucinations with a concurrent sharp increase in voriconazole blood concentration (C_{trough} 10.3 mg L^{-1}, target C_{trough} 1-5 mg L^{-1}). Neurotoxicity was considered to be related to voriconazole overexposure. The concentration of midostaurin was concomitantly six-fold above the average expected level, but without safety issues. Midostaurin was stopped and the dosage of voriconazole was adjusted with therapeutic drug monitoring. The evolution was favourable, with quick resolution and no recurrence of visual hallucinations. To our knowledge, this is the first case suggesting that midostaurin and voriconazole reciprocally inhibit each other's metabolism, leading to increased exposure of both. This case highlights the knowledge gap regarding drug-drug interactions between midostaurin and azole antifungals. Close clinical and therapeutic drug monitoring is advised in such cases.

KEYWORDS
acute myeloid leukaemia, cytochrome, drug-drug interaction, midostaurin, voriconazole

1 | INTRODUCTION

Midostaurin is an oral multikinase inhibitor approved in 2017 for the treatment of adult patients with fms-like tyrosine kinase 3 (FLT3)-mutated acute myeloid leukaemia (AML) and advanced systemic mastocytosis. For AML, it is given first in combination with standard chemotherapy, then alone as a maintenance therapy for up to 12 months in patients not undergoing allogeneic stem cell

transplantation.[1] Midostaurin is extensively metabolized by the cytochrome P450 (CYP) 3A4 in two major active metabolites (CGP62221 and CGP52421).[2] In vitro studies have shown that midostaurin and its metabolites are both inhibitors and inducers of several CYPs.[2] Thus, midostaurin is associated with a high potential for drug-drug interactions (DDIs), as a substrate (victim) but also as a perpetrator. However, so far little is known about midostaurin as a perpetrator of DDIs, as most pharmacokinetic (PK) studies have focused on midostaurin as a victim.[3] In one DDIs study, the concentrations of midostaurin were shown to be twice higher in AML patients treated with itraconazole compared to those without itraconazole.[2] In another DDIs study, midostaurin AUC increased 10-fold with ketoconazole.[4] In a case series, midostaurin trough concentrations (C_{trough}) were significantly increased in two patients co-treated with prophylactic posaconazole compared to those measured in patients without antifungal therapy or treated with isavuconazole.[5] Azole antifungals are frequently administered to patients with AML, either for aspergillosis prophylaxis or treatment. Posaconazole is indicated for prophylaxis, whereas voriconazole and isavuconazole are indicated for treatment.[6,7] Azoles metabolic pathways and DDIs potential differ.[3] Voriconazole has a strong potential for DDIs, as it is both a substrate and a strong inhibitor of CYP2C19, CYP2C9 and CYP3A4. In addition, it exhibits a nonlinear PK at high exposure levels.

We report a newly identified bidirectional DDI between midostaurin and voriconazole, focusing mainly on the role of midostaurin as a perpetrator of DDIs. Clinicians should be aware of this complex interaction to manage it appropriately and thus avoid safety issues.

2 | CASE PRESENTATION

A 49-year-old woman was diagnosed with AML harbouring FLT3-internal tandem duplication in July 2022. She received a first cycle of induction chemotherapy with daunorubicin 60 mg m^{-2} daily from day 1 (D1) to D3, cytarabine 200 mg m^{-2} daily from D1 to D7 and midostaurin 50 mg twice a day (bid) from D9 to D21 (last dose of midostaurin given on D22).

The patient developed invasive pulmonary aspergillosis while on fluconazole prophylaxis 400 mg daily from D5. This diagnosis was based on positive galactomannan serum immunoassay and new multiple dense, well-circumscribed pulmonary lesions on CT. Thus, fluconazole was replaced by voriconazole on D22 at standard dosage, with two intravenous (iv) loading doses of 6 mg kg^{-1} each (350 mg for 58 kg) followed by a maintenance dose of 4 mg kg^{-1} (230 mg) bid iv. The dosage of voriconazole was reduced to 200 mg bid iv as the C_{trough} measured on D28 was 5.3 mg L^{-1} (target C_{trough} 1-5 mg L^{-1}).[8] On D33, voriconazole and its main metabolite voriconazole-N-oxide C_{trough} values were 1.5 and 2.7 mg L^{-1}, respectively. Voriconazole and voriconazole-N-oxide plasma concentration measurements were performed at the Clinical Pharmacology Laboratory of Lausanne University Hospital (Switzerland) using a previously published method.[9] Blood samples were collected and centrifuged in EDTA-containing tubes. Plasma samples (100 µL) were subjected to protein precipitation with acetonitrile and supernatant dilution, and analysed by the multiplex ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method using the stable isotopically-labelled internal standards voriconazole-d3 and voriconazole-d3-N-oxide. The lower limits of quantification were 0.02 and 0.01 mg L^{-1}, respectively. The patient was discharged with a prescription of voriconazole 200 mg bid per os (po).

The patient was readmitted for a second cycle of induction with daunorubicin 60 mg m^{-2} daily from D43 to D45, cytarabine 1000 mg m^{-2} bid from D43 to D49 and midostaurin 50 mg bid planned from D51 to D64. Midostaurin was stopped prematurely on D57 due to suspicion of pulmonary toxicity (not subsequently confirmed) and concurrent supratherapeutic concentration. Midostaurin, CGP62221 and CGP52421 C_{trough} values with their respective reference values (geometric mean and variability expressed as CV%) were midostaurin 15.7 mg L^{-1} (2.4 mg L^{-1}, 112%), CGP62221 0.8 mg L^{-1} (2.4 mg L^{-1}, 76%) and CGP52421 6.3 mg L^{-1} (2.6 mg L^{-1}, 52%).[2] For midostaurin and its metabolites (CGP62221 and CGP52421), the plasma samples were subjected to protein precipitation with organic solvents and analysed by UPLC-MS/MS method. Internal standards included the stable isotopically labelled commercial substances for all analytes. The lower limits of quantification for midostaurin, CGP62221 and CGP52421 were 0.14, 0.06 and 0.09 mg L^{-1}, respectively (unpublished validated method).

Voriconazole C_{trough} was initially low (1.0 mg L^{-1} on D43 and 0.4 mg L^{-1} on D49), thus its dosage was increased to 250 mg bid po on D50. A steep increase in C_{trough} was then observed at 4.1 mg L^{-1} on D54 and 10.3 mg L^{-1} on D59. The patient presented visual hallucinations from D57 but no other adverse reaction was observed (normal neurological examination and QTc interval). Liver blood tests were within normal reference ranges, except gamma-glutamyl transferase (74 U L^{-1}, normal range 6-42 U L^{-1}). Voriconazole was withheld for 36 h and resumed at 125 mg bid po on D61. The dosage was further reduced to 75 mg bid po as C_{trough} was still 8.7 mg L^{-1} on D63. Only from D66 onwards could the exposure be maintained within the therapeutic interval (last C_{trough} 2.6 mg L^{-1} with voriconazole 200 mg bid). Of interest, the ratio of voriconazole to its main metabolite voriconazole-N-oxide inverted during midostaurin exposure and shortly after compared to periods without midostaurin (Figure 1). Apart from voriconazole and midostaurin, the patient did not receive any other CYP inhibitors or inducers, except clarithromycin (1 g) on D58 for suspected pneumonia.

The evolution was favourable with resolution and no recurrence of visual hallucinations, stabilization of pulmonary aspergillosis and complete hematologic response on the bone marrow biopsy, allowing consideration of an allogeneic stem cell transplantation, which the patient refused. She relapsed at 5.5 months and was treated with hydroxycarbamide and gilteritinib.

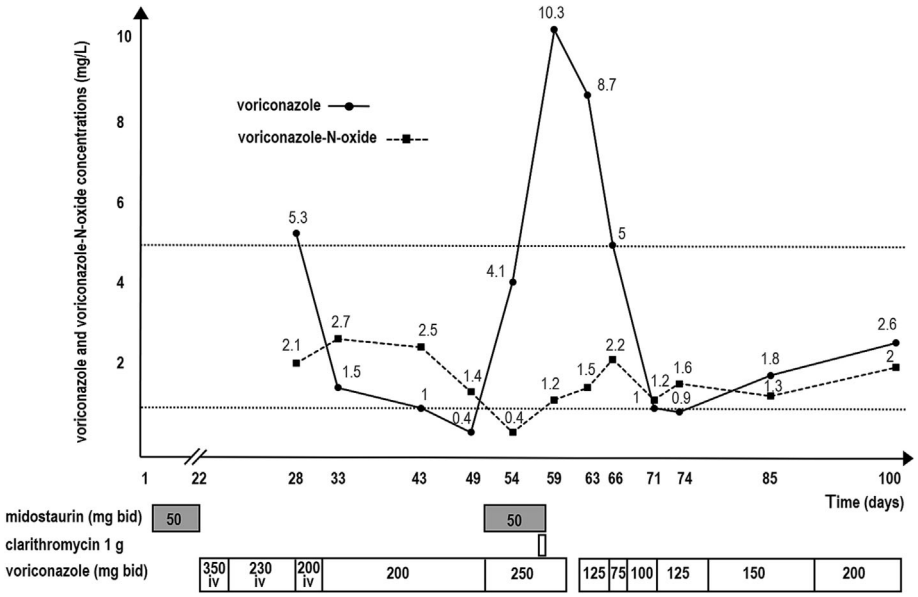

FIGURE 1 Therapeutic drug monitoring of voriconazole. The solid line represents voriconazole trough concentrations and the dashed line voriconazole-N-oxide, its main metabolite. The dotted lines define the upper and lower limits of voriconazole target trough concentrations (1-5 mg L^{-1}). Dosages of voriconazole and midostaurin over time are indicated by white and grey rectangles, respectively. The route of administration is oral unless otherwise specified. The timeline starts from day 1, which is the first day of the induction chemotherapy.

3 | DISCUSSION

Midostaurin is the first agent having shown survival benefit when combined with chemotherapy in FLT3 mutated AML.[10] Internal tandem duplication is a common FLT3 mutation, associated with unfavourable prognosis attributed to constitutive activation of FLT3 which promotes proliferation and survival of blast cells.[11] Midostaurin is a multikinase inhibitor, including FLT3.[12] Its main adverse reactions are myelosuppression and infections.

Midostaurin is metabolized by CYP3A4 in two major active metabolites, CGP62221 and CGP52421. Their elimination half-lives are 21, 32 and 482 h, respectively. The pharmacokinetic profile of midostaurin is atypical in that midostaurin C_{trough} increases initially up to D7 and decreases thereafter until reaching steady state at D28. CGP62221 has a similar behaviour whereas CGP52421 C_{trough} keeps increasing for more than 1 month. This pharmacokinetic profile is likely explained by a progressive reduction in the half-life due to the auto-induction of CYP3A4 causing the initial accumulation to decrease.[13]

In vitro, midostaurin caused a potent inhibition of CYP2C9, CYP3A, CYP1A2, CYP2C8, CYP2D6 and CYP2E1 at therapeutic concentrations (half-maximal inhibitory concentration [IC_{50}] values 0.3-2.9 mg L^{-1}). CGP62221 strongly inhibited CYP2C9, CYP3A, CYP1A2 and CYP2C8 (IC_{50} < 2.9 mg L^{-1}) while CGP52421 caused a strong inhibition of CYP3A and CYP2D6 (IC_{50} 1.1 to 2.9 mg L^{-1}) and a moderate inhibition of CYP2C9, CYP1A2 and CYP2C8 (IC_{50} 2.9 to 25.6 mg L^{-1}) at therapeutic concentrations. Inhibition was shown to be time-dependent (irreversible) for CYP3A. In vitro, midostaurin and its metabolites also showed inducing effects on several CYPs, including CYP2C19, CYP2C9 and CYP3A4.[14,15]

In a study with 18 healthy volunteers, midostaurin at a single 100 mg dose followed by repeated 50-mg doses bid over 3 days did not significantly alter the concentrations of midazolam (sensitive CYP3A4 substrate) or its metabolite 1′-hydroxymidazolam. The authors concluded that midostaurin did not inhibit or induce CYP3A4 in vivo. However, it should be emphasized that this study could not capture the inhibitory or inducing potential of midostaurin and its metabolites given that inhibition was tested after one single midostaurin dose, well before accumulation, and induction was tested well before steady state, when maximal induction is expected.[4]

In a physiologically based pharmacokinetic modelling study, the midazolam area under the curve (AUC) and peak plasma concentration (C_{max}) were predicted to increase by 20% with a single 100 mg dose of midostaurin. Conversely, midazolam AUC and C_{max} were predicted to decrease by 41% and 22% after multiple doses of midostaurin (50 mg bid for 28 days), suggesting an inducing effect on CYP3A4 at steady state.[16] Unfortunately, these two studies did not evaluate the effect of midostaurin on the two other CYPs involved in the metabolism of voriconazole, ie, CYP2C19 and CYP2C9.

The literature reports only one case in which midostaurin was identified as a perpetrator of DDIs. This case describes the DDI between cyclosporin (victim) and midostaurin in a 69-year-old patient undergoing allogeneic stem cell transplantation for FLT3-ITD + AML. Shortly after initiating midostaurin, cyclosporin C_{trough} increased by 70%, which was attributed to CYP3A4 inhibition by midostaurin.[17]

Our case also indicates that midostaurin is not only a victim but can also act as a perpetrator of DDIs. The inhibition of CYP2C9 and CYP3A4 involved in voriconazole metabolism by midostaurin and its metabolites resulted in supratherapeutic voriconazole levels and typical related toxicity signs (visual hallucinations). Clarithromycin had likely no significant impact on voriconazole PK as it was administered just 1 day and it only inhibits CYP3A4. Inhibition of voriconazole metabolism is supported by the increase in voriconazole/metabolite ratio during midostaurin exposure and on subsequent days. The sustained high concentrations of voriconazole for several days after dosage reduction are consistent with the nonlinear kinetics of voriconazole at high exposure. Reciprocally, the strong CYP3A4 inhibitor voriconazole increased midostaurin concentrations by approximately six-fold above the average expected level, but without obvious safety

issues. Using the Drug Interaction Probability Scale (DIPS),[18] the DDI between midostaurin and voriconazole is scored as probable. To our knowledge, this is the first case suggesting that midostaurin and voriconazole reciprocally inhibit each other's metabolism, leading to increased exposure of both. Although not specifically studied, the DDIs between midostaurin and posaconazole or isavuconazole are expected to be unidirectional on the basis of their pK characteristics: posaconazole is likely to increase midostaurin AUC,[5] while midostaurin may increase isavuconazole AUC. Thus, isavuconazole may be a better option for the treatment of invasive aspergillosis in a patient treated with midostaurin, as it has fewer DDIs than voriconazole.[19] This case highlights the knowledge gap for the appropriate management of the DDIs between midostaurin and antifungals since patients treated with midostaurin are often co-treated with azoles for prophylaxis or treatment. In conclusion, close clinical and therapeutic drug monitoring is advised for the management of such complex critical DDIs.[19]

3.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[20]

AUTHOR CONTRIBUTIONS

David Haefliger drafted the manuscript. Catia Marzolini was involved in the analysis of drug-drug interactions and critical revision of the manuscript. Frederic Lamoth was involved in patient care and critical revision of the manuscript. Thomas Pabst was involved in midostaurin plasma concentration measurement and critical revision of the manuscript. Thierry Buclin was involved in critical revision of the manuscript. Francoise Livio drafted the manuscript and revised the final version.

ACKNOWLEDGEMENTS

Open access funding provided by Universite de Lausanne.

CONFLICT OF INTEREST STATEMENT

C.M. has received speaker honoraria from MSD, ViiV and Pfizer unrelated to this work. F.L. has received research funding from Pfizer, MSD, Gilead and Novartis, and speaker honoraria from Pfizer, Gilead, MSD and Mundipharma. All contracts were made with and fees paid to his institution (Lausanne University Hospital-CHUV). The other authors have no potential conflicts to disclose.

CONSENT

The patient provided written informed consent to publish this report.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Haefliger D, Marzolini C, Lamoth F, Pabst T, Buclin T, Livio F. Clinically relevant bidirectional drug-drug interaction between midostaurin and voriconazole. *Br J Clin Pharmacol*. 2023;1-5. doi:10.1111/bcp.15743