Management of Venetoclax-Posaconazole Interaction in Acute Myeloid Leukemia Patients: Evaluation of Dose Adjustments

Suresh K. Agarwal, PhD[1]; Courtney D. DiNardo, MD[2]; Jalaja Potluri, MD[1]; Martin Dunbar, DrPH[1]; Hagop M. Kantarjian, MD[2]; Rod A. Humerickhouse, MD, PhD[1]; Shekman L. Wong, PhD[1]; Rajeev M. Menon, PhD[1]; Marina Y. Konopleva, MD, PhD[2]; and Ahmed Hamed Salem, PhD[1,3]

[1]AbbVie Inc, North Chicago, Illinois; [2]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas; and [3]Department of Clinical Pharmacy, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt

ABSTRACT

Purpose: The effect of posaconazole, a strong cytochrome P450 3A (CYP3A) inhibitor and commonly used antifungal agent, on the pharmacokinetic properties of venetoclax, a CYP3A substrate, was evaluated in patients with acute myeloid leukemia to determine the dose adjustments needed to manage this potential interaction.

Methods: Twelve patients received 20- to 200-mg ramp-up treatment with oral venetoclax and 20 mg/m^2 of intravenous decitabine on days 1 through 5, followed by 400 mg of venetoclax alone on days 6 through 20. On days 21 through 28, patients received 300 mg of posaconazole plus reduced doses of venetoclax (50 or 100 mg) to account for expected increases in venetoclax plasma concentrations. Blood samples were collected before dosing and up to 24 hours after the venetoclax dose on days 20 and 28.

Findings: Compared with a venetoclax dose of 400 mg when administered alone (day 20), coadministration of venetoclax at a 50-mg dose with multiple doses of posaconazole increased mean venetoclax C_{max} and $AUC_{0–24}$ by 53% and 76%, respectively, whereas coadministration of venetoclax at a 100-mg dose with posaconazole increased mean venetoclax C_{max} and $AUC_{0–24}$ by 93% and 155%, respectively. When adjusted for different doses and nonlinearity, posaconazole was estimated to increase venetoclax C_{max} and $AUC_{0–24}$ by 7.1- and 8.8-fold, respectively. Both the 50- and 100-mg venetoclax doses administered with posaconazole were well tolerated.

Implications: The results are consistent with inhibition of CYP3A-mediated metabolism of venetoclax. Posaconazole can be used for antifungal prophylaxis in patients with acute myeloid leukemia receiving venetoclax after reducing the venetoclax dose by at least 75%. ClinicalTrials.gov identifier: NCT02203773. (*Clin Ther.* 2017;39:359–367)

Key words: ABT-199/GDC-0199, BCL-2, CYP3A, pharmacokinetic interaction, posaconazole, venetoclax.

INTRODUCTION

Venetoclax (ABT-199/GDC-0199) is a potent, selective, B-cell lymphoma 2 (BCL-2) inhibitor that has recently been approved by the US Food and Drug Administration for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion who have received at least 1 prior therapy.[1,2] The efficacy of venetoclax in this population has been found in a multicenter study of 116 CLL patients with 17p deletion who had symptomatic relapsed or refractory disease, highlighting the potential of BCL-2 antagonism as a therapeutic strategy in relapsed or refractory CLL.[3] The efficacy of venetoclax, either as monotherapy or in combination with other agents, appears to extend to other hematologic malignancies

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in which overexpression of BCL-2 contributes to tumor pathogenesis, as evidenced by promising preliminary efficacy results in patients with non-Hodgkin lymphoma (NHL), multiple myeloma (MM), and acute myeloid leukemia (AML).[3–10]

The pharmacokinetic and pharmacodynamic properties of venetoclax have been characterized in several clinical studies.[11–18] Venetoclax plasma concentrations peaked approximately 5 to 8 hours after dosing under low fat conditions, exposures increased 3- to 5-fold in the presence of food, and the terminal phase $t_{1/2}$ ranged from 14.1 to 18.2 hours in patients with CLL and NHL. The results of in vitro and clinical drug interaction studies revealed a need to either modify the dose of venetoclax when it is coadministered with strong or moderate cytochrome P450 3A (CYP3A) inhibitors or inducers or consider alternative medications.[13,19,20]

Patients with AML and other hematologic malignant tumors are at a high risk for febrile neutropenia and life-threatening fungal infections.[21] To reduce the likelihood and severity of fungal infections, antifungal prophylaxis with azole compounds (ie, fluconazole or posaconazole) is the standard of care.[22] However, azole compounds carry a risk of drug-drug interactions because of their effects on CYP enzymes and transporter proteins.[23]

Posaconazole is superior to other azole agents in the prevention of invasive fungal infections in neutropenic patients with AML.[22] Previous experience with venetoclax in relapsed or refractory AML in which venetoclax was dosed as a single agent at 800 and 1200 mg revealed venetoclax activity and acceptable tolerability in AML patients.[9] In the present study, posaconazole was introduced to venetoclax and decitabine combination treatment under carefully controlled conditions. The study aimed to address the medical need for fungal prophylaxis in AML patients treated with venetoclax by identifying venetoclax dosing regimens that are safe, effective, and well tolerated.

PATIENTS AND METHODS

The posaconazole drug-drug interaction (DDI) study was conducted as a substudy within an ongoing Phase Ib open-label study of venetoclax combined with decitabine or azacitidine in treatment-naive patients with AML (NCT02203773). The DDI substudy was conducted at a single site (The University of Texas MD Anderson Cancer Center, Houston, TX) in accordance with Good Clinical Practice guidelines and the ethical principles that have their origin in the Declaration of Helsinki. The protocol and informed consent form were approved by the institutional review board at the University of Texas MD Anderson Cancer Center, and each patient provided written informed consent.

Patients

Adult men and women at least 65 years of age with newly diagnosed histologically confirmed AML by World Health Organization criteria,[24] ineligible for treatment with standard induction therapy with cytarabine and anthracycline, and with an Eastern Cooperative Oncology Group performance score of 0 to 2 were eligible to enroll. Key inclusion criteria included adequate cardiovascular, renal, and hepatic function and a white blood cell count $<25 \times 10^9$/L. Key exclusion criteria included the presence of favorable risk cytogenetics (t[8;21], inv[16], or t[15;17]), known active central nervous system involvement from AML, or evidence of clinically significant uncontrolled conditions, including but not limited to systemic infection requiring intravenous (IV) antimicrobial therapy. Patients must not have used moderate or strong inducers or inhibitors of CYP3A or consumed grapefruit, grapefruit products, Seville oranges, or star fruit within 3 days of the initiation of study treatment.

Study Design and Dosing Scheme

The posaconazole DDI substudy enrolled 12 patients. All patients received oral venetoclax at an escalating dose of 20 to 200 mg and IV decitabine 20 mg/m^2 on days 1 through 5 (ramp-up phase), followed by 400-mg venetoclax monotherapy on days 6 through 20. On days 21 through 28, patients received a predetermined reduced venetoclax dose (50 or 100 mg once daily to account for the expected increase in venetoclax plasma concentrations) with 300 mg of oral posaconazole twice on day 21 and once daily on days 22 through 28 (Figure 1). The posaconazole dosage regimen for this study was the same as its labeled regimen of 300 mg twice on the first day and 300 mg once a day starting on the second day for prophylaxis of fungal infections. Because posaconazole was reported to