Antifungal Prophylaxis with Posaconazole in Patients with Acute Myeloid Leukemia: Dose Intensification Coupled with Avoidance of Proton Pump Inhibitors Is Beneficial in Shortening Time to Effective Concentrations

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This study aimed to assess the influence of dose frequency and the presence or absence of cotreatment with proton pump inhibitors (PPIs) on the time to a target trough concentration ($C_{\min}$) of >700 ng/ml with posaconazole in the first 8 days of antifungal prophylaxis in hematological patients. This was a retrospective, observational study performed with 42 adult patients with acute myeloid leukemia who underwent posaconazole prophylaxis with 200 mg every 8 h (q8h) or 200 mg q6h after receiving induction chemotherapy and who had at least three subsequent therapeutic drug monitoring assessments during the first 8 days of treatment. The cohort was split into four groups (group 1, 200 mg q8h without PPI; group 2, 200 mg q8h with PPI; group 3, 200 mg q6h without PPI; group 4, 200 mg q6h with PPI). Rapid attainment of the target $C_{\min}$ was obtained only in group 3 ($P < 0.01$) (median $C_{\min}$ on day 4 of 935.5 ng/ml [interquartile range, 760.0 to 1,270.0 ng/ml] in group 3, versus 567.0 ng/ml [346 to 906 ng/ml] in group 1, 420.0 ng/ml [326.2 to 527.2 ng/ml] in group 2, and 514.0 ng/ml [403.7 to 564.7 ng/ml] in group 4). A linear accumulation of posaconazole over time was observed among patients in groups 1 and 3, regardless of the total daily dosage, differently from what occurred among those receiving PPI cotreatment (groups 2 and 4). Dose intensification (200 mg q6h) coupled with avoidance of PPI coadministration may represent a very powerful strategy to rapidly achieve effective concentrations with posaconazole in neutropenic hematological patients.

Posaconazole is a second-generation triazole antifungal agent with a broad spectrum (1) that is currently licensed for prophylaxis in hematological patients at high risk of invasive fungal infections (2, 3).

Rapid attainment of effective posaconazole concentrations during the neutropenic phase may be of paramount importance, considering that this is the most vulnerable period for mold infections in hematological patients (4). Unfortunately, the currently available oral formulation of posaconazole has an unpredictable pharmacokinetic behavior, and therapeutic drug monitoring (TDM) of trough plasma concentrations ($C_{\min}$) is being increasingly advocated for guidance of appropriate drug exposure with posaconazole over time (5–7).

As far as the therapeutic range for posaconazole is concerned, some authors suggest a $C_{\min}$ of >500 ng/ml as a target threshold (8), whereas others found evidence to support a more conservative $C_{\min}$ of >700 ng/ml (9), although a definitive threshold is still to be defined. Achievement of the desired threshold with the current posaconazole formulation is quite challenging, considering that several factors were shown to affect its absorption rate (10).

Various strategies have been suggested in order to improve its oral bioavailability, among which avoidance of drugs altering gastric acidic pH, taking posaconazole with a high-fat meal, and increase of dose frequency are considered the most clinically relevant (11). Of note, these approaches are not always simultaneously feasible for the same patient, and what remains to be answered is the role that these approaches may have in shortening the time to therapeutically relevant concentrations in daily clinical practice.

The aim of this study was to assess the relative influence that

dose frequency and the presence or absence of cotreatment with proton pump inhibitors (PPIs) had on the time to a target $C_{\min}$ of >700 ng/ml in a population of hematological patients who received posaconazole prophylaxis after induction chemotherapy for acute myeloid leukemia.

MATERIALS AND METHODS

Study design. This was an observational study which involved adult patients with acute myeloid leukemia who underwent antifungal prophylaxis with posaconazole in the period between August 2009 and November 2010 after receiving induction chemotherapy at the hematologic clinic of our university teaching hospital. During this period, posaconazole prophylaxis was carried out with 2 dosing regimens at the physician's discretion, namely, 200 mg every 8 h (q8h) or 200 mg q6h, with the latter regimen usually being preferred in cases of very severe neutropenia. Concomitant use of PPIs was discouraged as much as possible.

Only patients who had at least three subsequent $C_{\min}$ assessments during the first 8 days of treatment according to our routine TDM program were considered feasible for this study. Blood samples for TDM were collected immediately before the morning administration and after centrifuged plasma samples were analyzed by means of a validated liquid chromatography-tandem mass spectrometry method (12). The intra- and

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TABLE 1 Patient demographic and clinical characteristics

	Value for group				
Variable ^a	1 (<i>n</i> = 10)	2 (<i>n</i> = 11)	3 (<i>n</i> = 10)	4 (<i>n</i> = 11)	<i>P</i> value
Demographics					
Mean age (yr) ± SD	52.3 ± 18.2	40.1 ± 18.9	44.7 ± 17.5	44.1 ± 12.9	0.80
No. of male patients/no. of female patients	3/7	7/4	5/5	4/7	0.41
Median wt (kg) (IQ range)	73.0 (62.6–74.7)	65.0 (50.0–75.7)	66.5 (55.0–85.0)	72.0 (60.7–80.0)	0.53
Median BMI (kg/m ²) (IQ range)	25.1 (23.5–27.0)	23.7 (17.7–25.8)	22.9 (18.7–27.3)	24.4 (23.4–28.9)	0.07
Baseline laboratory parameters					
Median AST level (IU/liter) (IQ range)	14 (12–18)	20 (11–30)	17 (14–27)	15 (10–23)	0.42
Median ALT level (IU/liter) (IQ range)	14 (11–27)	29 (21–32)	23 (16–28)	23 (14–20)	0.23
Median γ-GT level (IU/liter) (IQ range)	30 (21–62)	62 (32–73)	63 (25–313)	39 (18–77)	0.33
Median albumin level (g/liter) (IQ range)	32.0 (31.2–36.2)	34.4 (32.3–36.3)	32.5 (32.1–33.6)	33.8 (31.0–35.3)	0.86
Posaconazole prophylaxis					
Dosing regimen	200 mg q8h	200 mg q8h	200 mg q6h	200 mg q6h	
Mean duration of treatment (days) ± SD	17.8 ± 8.5	17.7 ± 7.5	17.7 ± 9.8	14.7 ± 4.5	0.88
Coadministered PPI	No	Yes	No	Yes	
Omeprazole 40 mg i.v.	0	4	0	5	
Pantoprazole 20 mg <i>per os</i>	0	7	0	6	
No. of patients with underlying condition					
Mucositis (grades II to III)	0	2	1	4	0.14
Diarrhea (grades II to III)	0	1	0	0	
Vomiting	0	0	0	0	
No. of patients in compliance with food intake ^b					
High compliance	9	10	10	9	0.57
Low compliance	1	1	0	2	0.57

^a i.v., intravenous.^b Patients with high or low compliance consumed on average >50% or $\leq$ 50% high-fat meals concomitantly with posaconazole administration, respectively.

interday coefficients of variation of the method were <5%, with a lower limit of detection of 15 ng/ml.

Data on patient characteristics (age, weight, height, and body mass index [BMI]), hepatic and renal function (alanine aminotransferase [ALT], aspartate transaminase [AST], gamma-glutamyl transferase [γ -GT], albumin, creatinine, and bilirubin levels), compliance in taking posaconazole with a high-fat meal, presence or absence of cotreatment with a PPI or with any other drug which might have reduced posaconazole absorption, and the presence of underlying gastrointestinal conditions which might have potentially affected posaconazole absorption (mucositis, diarrhea, and vomiting) were retrieved. Appearance of fungal infections during antifungal prophylaxis was checked.

The retrospective cohort was split into four groups according to the total daily dosing regimen of posaconazole (200 mg q8h or q6h) and the presence or absence of cotreatment with PPIs (omeprazole or pantoprazole), with the intent of assessing the relative influence that these factors might have on the time to effective concentrations (group 1, 200 mg q8h without PPI; group 2, 200 mg q8h with PPI; group 3, 200 mg q6h without PPI; group 4, 200 mg q6h with PPI).

The study was approved by the Ethical Committee of the Azienda Ospedaliero-Universitaria Santa Maria della Misericordia of Udine.

Statistical analysis. The Kolmogorov-Smirnov test was used to assess the normal or nonnormal distribution of data, and accordingly, means $\pm$ standard deviations or medians and 25th to 75th interquartile ranges were used for statistic descriptions. A one-way analysis of variance was used to compare continuous data among groups, whereas a χ -square test was used for categorical variables. A *P* value of <0.05 was required to achieve statistical significance. The statistical analysis was performed with SigmaStat version 3.1.

RESULTS

The 42 patients who represented the retrospective cohort were almost equally distributed in the four identified groups and had similar demographics and clinical characteristics, which are described in Table 1. Grade II to III mucositis and/or diarrhea occurred in only a minority of cases, and the overall level of patient compliance in consuming posaconazole with a high-fat meal was high. None of the patients received any other agents, other than PPI, which might have potentially reduced posaconazole absorption.

Trends of posaconazole $C_{\min}$ over the first 8 days of treatment in the various groups are depicted in Fig. 1. On day 2, median $C_{\min}$ values were subtherapeutic in all of the assessable groups, with no statistically significant difference (*P* = 0.207). Interestingly, on day 4, attainment of a therapeutically effective median $C_{\min}$ was documented only for group 3, with significantly higher values than those of the other groups (*P* < 0.01) (median $C_{\min}$ of 935.5 ng/ml [interquartile {IQ} range, 760.0 to 1,270.0 ng/ml] in group 3 versus 567.0 ng/ml [346 to 906 ng/ml] in group 1, 420.0 ng/ml [326.2 to 527.2 ng/ml] in group 2, and 514.0 ng/ml [403.7 to 564.7 ng/ml] in group 4). This difference became even more relevant on day 8 (median $C_{\min}$ of 1,550.0 ng/ml [IQ range, 1,335.0 to 1,960.0 ng/ml] in group 3 versus 884.5 ng/ml [701.0 to 1,280.0 ng/ml] in group 1, 716.0 ng/ml [450.3 to 1,150.0 ng/ml] in group 2, and 589.0 ng/ml [364.5 to 805.8 ng/ml] in group 4 [*P* = 0.006]).

Of note, when looking at the trend of posaconazole accumula-

FIG 1 Median and 25th- to 75th-percentile range of posaconazole C_{min} s on days 2, 4, and 8 of antifungal prophylaxis for the four groups (group 1, 200 mg q8h without PPI; group 2, 200 mg q8h with PPI; group 3, 200 mg q6h without PPI; group 4, 200 mg q6h with PPI).

tion in plasma over time, whereas a proportional linear increase in C_{min} was observed among those patients receiving posaconazole in the absence of PPI cotreatment (groups 1 and 3), conversely, no such relationship was found among those receiving PPI cotreatment (groups 2 and 4).

From a clinical viewpoint, 1 out of 42 patients experienced invasive fungal infections while on posaconazole prophylaxis (proven fungemia by *Fusarium solani*), who was successfully treated with voriconazole.

DISCUSSION

This retrospective study is the first to directly compare the influence of dose intensification of posaconazole and the absence or presence of PPI cotreatment on time to therapeutically effective posaconazole C_{min} in hematological patients.

Our findings show that administration of posaconazole with a daily dosing regimen of 200 mg q6h in the absence of PPIs may represent a very valuable strategy to attain a C_{min} of >700 ng/ml within the first 4 days of antifungal prophylaxis among adult patients with acute myeloid leukemia.

A rapid attainment of prophylactic plasma concentrations in neutropenic patients could be a valuable approach in order to avoid the risk of breakthrough infection due to underexposure. However, this is quite challenging with posaconazole, considering that with the current formulation, the drug accumulates slowly in plasma due to saturable absorption and a high volume of distribution (13).

Few works have investigated the plasma concentration profile of posaconazole during the first week of treatment with the standard dosage of 200 mg q8h. Both a Monte Carlo simulation (6) and an observational study (14) showed that the expected median C_{min} at day 7 was <500 ng/ml (350 and 440 ng/ml, respectively). Cornely et al. reported that among 61 acute leukemic myelogenous patients not taking PPIs, the median C_{min} achieved values higher than this threshold (620 ng/ml) only from day 8 onward (15).

Worryingly, recent evidence from daily clinical practice suggests that the standard dosing regimen of 200 mg q8h may fre-

quently be insufficient in ensuring valuable concentrations even at steady state (C_{ss}). C_{ss} values of <500 ng/ml were reported in several cases with this regimen by various authors (in 79.6% of cases [16], in 76.2% of cases [17], and in 44% of cases [18]). Likewise, when considering the threshold of 700 ng/ml, even higher percentages of cases with subtherapeutic C_{ss} values were reported (in 85.2% of cases [16], in 90.5% of cases [17], in 70.3% of cases [19], in 48% of cases [20], and in 20% of cases [21]). Of note, it should not be overlooked that most of those studies considered either patients taking posaconazole alone or those taking it concomitantly with PPIs or with H_2 antagonists (22), which are known to impair the posaconazole absorption rate.

Unfortunately, administration of acidic suppressor agents is a relatively frequent occurrence among hematological patients, and several studies highlighted the negative influence that the concomitant use of these drugs may have on posaconazole exposure in clinical practice. Alfenaar et al. (23) first reported the case of one patient in whom posaconazole plasma concentrations were almost halved when omeprazole was added. Likewise, similar findings were also shown with cimetidine (24). Of note, it was shown that even in healthy volunteers, the coadministration of esomeprazole may completely counteract the net increase in posaconazole plasma exposure achievable when taking the drug with acidic carbonated beverages versus under fasting conditions (25, 26).

Although conflicting data on this topic still exist in the literature (14, 27), it should be noticed that in a study assessing posaconazole exposure after standard dosages in relation to the use or nonuse of pantoprazole in hematological patients, significantly lower median C_{min} values were reported for patients taking this PPI than for those who did not (630 and 1,125 ng/ml, respectively) (20).

Besides maintenance of acidic gastric pH and taking posaconazole with a high-fat meal (28), another valuable strategy for attainment of higher posaconazole concentrations may be dose intensification by shortening the dosing interval to 6 h (29). Ezzet et al. (10) first estimated that in healthy volunteers, when considering a total daily dose of 800 mg for posaconazole, the more frequent administration of small refracted doses (200 mg q6h) may ensure a much higher average C_{ss} (517 ng/ml) than those achievable with a single daily dose of 800 mg (162 ng/ml) or with two separate doses of 400 mg q12h (320 ng/ml). Likewise, Krishna et al. (25), when assessing posaconazole exposure in healthy subjects after administration of the same total daily dose for 7 days under various conditions (200 mg q6h alone, 200 mg q6h with nutritional supplement, 400 mg q12h alone, and 400 mg q12h with nutritional supplement), found that the more refracted dosage under fasting conditions ensured the highest mean area under the concentration-time curve (AUC).

Our findings are in agreement with the latter studies and highlight that the regimen of 200 mg q6h may ensure valuable prophylactic exposure within the first 4 days of treatment with posaconazole in patients with acute myeloid leukemia, provided that coadministration of PPIs is strictly avoided. Of note, PPI cotreatment counteracted the expected benefit in drug exposure derived from the intensified daily dosage in group 4, as no increase in the median C_{ss} was observed ($P = 0.15$).

We recognize that our study has some limitations. First, this is an observational retrospective study with a relatively small sample size in which the number of TDM measurements per patient was

variable. This could limit the generalizability of our data. Second, the presence of underlying mucositis and/or diarrhea among some patients in groups 2, 3, and 4 but not among those in group 1 might have partially affected our analysis. For example, the more frequent occurrence of mucositis in group 4 might partially explain why the median posaconazole concentration on day 8 was lower in this group than in group 2 although not significantly. Third, the fact that the total daily dosages of posaconazole as well as the PPI cotreatment (in terms of the selected agent and administered dosage) were applied at the physician's discretion, which might have contributed to an increase in variability.

In conclusion, considering that oral absorption of the currently available formulation of posaconazole in hematological patients is quite challenging, it remains of foremost importance to identify strategies useful to ensure optimal exposure within clinically useful time frames (11, 29). We believe that a daily regimen of 200 mg q6h coupled with avoidance of PPI coadministration may represent a powerful strategy to rapidly achieve effective concentrations with posaconazole.

Clearly, a better knowledge of the relative impact of different factors in preventing posaconazole underexposure should not discourage physicians from relying on TDM for dose optimization, whenever possible.

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