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# Therapeutic Drug Monitoring of Posaconazole in Patients with Acute Myeloid Leukemia or Myelodysplastic Syndrome

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**Posaconazole is a broad-spectrum triazole antifungal available as an oral suspension. Pharmacokinetic data showed a high variability of plasma posaconazole concentrations (PPCs) in patients, suggesting a potential interest in drug monitoring. The aim of our prospective study was to measure the PPCs in prophylactically treated patients to evaluate the impact of different factors on these concentrations. In 40 patients treated prophylactically with posaconazole for acute myeloid leukemia or myelodysplastic syndrome between February 2009 and August 2010, PPCs were measured at day 7 of treatment and then twice weekly. Demographic data, clinical data (including gastrointestinal disorders, comedications, and treatment compliance), caloric and fat intake, and biological data were collected and evaluated. We obtained 275 measurements of PPCs, with a median of 430 ng/ml. PPCs were significantly lower in patients with mucositis ($P < 0.001$), nausea ($P = 0.03$), diarrhea ($P = 0.03$), or vomiting ($P = 0.05$). PPCs were higher in patients with a higher caloric intake ($P = 0.02$), while the proportion of fat intake had no influence on PPCs ($P = 0.84$). The concomitant use of proton pump inhibitors decreased the PPCs ($P = 0.02$), while the use of tacrolimus increased the PPC ($P = 0.03$). In the multivariate analysis, the factors influencing the PPCs independently were the concomitant use of tacrolimus ($P < 0.001$), the presence of mucositis ($P = 0.01$), and food intake ($P = 0.02$). Our study confirmed the high variability of posaconazole bioavailability and showed the significant influence of gastrointestinal disorders, food intake, and concomitant medication on the PPCs. However, the optimal PPCs still remain to be defined and correlated with clinical efficacy.**

Invasive fungal infections (IFI) remain an important cause of morbidity and mortality in immunocompromised patients. Their incidence has significantly increased over the last 2 decades (17, 18). Thus, it is mandatory to optimize strategies for prevention, diagnosis, and treatment of these infections.

Posaconazole is a broad-spectrum triazole antifungal with good activity against most *Candida* and *Aspergillus* species. It is also active against emerging pathogens more resistant to classical antifungals, like *Fusarium* or *Zygomycetes* (17, 18). The drug is approved for antifungal prophylaxis in neutropenic patients after induction chemotherapy for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) and for patients treated with corticosteroids for graft-versus-host disease after allogeneic hematopoietic stem cell transplantation (4, 23). It is also available for the treatment of invasive aspergillosis in patients who are refractory or intolerant to standard therapy (24).

Pharmacokinetic studies of posaconazole in healthy volunteers and patients have shown great interindividual variability of PPCs, independent of age, sex, weight, or ethnic origin (10, 12, 13, 20, 22). Furthermore, several studies suggest a relationship between PPCs and prophylactic (12, 13) or therapeutic (24) efficacy. However, the exact role of posaconazole monitoring remains to be defined more precisely. The main objective of our prospective study was to measure PPCs in prophylactically treated patients to evaluate the impact of different factors encountered in daily practice on these concentrations.

## MATERIALS AND METHODS

**Study setting and patient enrollment.** This was a prospective, bicentric study, carried out at Institute J. Bordet's and Erasme Hospital's hematology departments between February 2009 and August 2010. Patients were eligible to participate if they were aged 16 years or older and if they were treated prophylactically with posaconazole during chemotherapy for acute myeloid leukemia or myelodysplastic syndrome.

**Posaconazole administration.** The daily administered dose of posaconazole was 200 mg (i.e., 5 ml of oral suspension) three times a day, during meals containing whenever possible 50 g of fat. The nutrition staff tailored patients' meals according to their food preferences.

Prophylaxis was started on the first day of chemotherapy and continued until recovery from neutropenia (neutrophil count, $>1{,}000/mm^3$) or until another antifungal agent was administered, either prophylactically if the patient was intolerant to posaconazole or therapeutically in case of an IFI. IFIs were defined as proven, probable, or possible, according to the 2008 European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) (7). Patients could participate in the study during several episodes of treatment depending on the number of chemotherapies administered or whether an interruption of the posaconazole treatment had occurred, followed by a restart of the treatment.

**Blood sampling.** From the 7th day of treatment (corresponding to the steady state) onwards, blood samples were collected twice a week until treatment discontinuation: one blood sample was taken before the first daily dose of posaconazole (time zero [T0]) and another 5 h after that first dose (time 5 [T5]) (corresponding to the maximum plasma concentration[$C_{max}$]).

**Plasma posaconazole concentration (PPC) determination.** Plasma posaconazole was measured by high-performance liquid chromatography (HPLC) with UV detection (260 nm) in the clinical chemistry laboratory

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at Erasme Hospital. Briefly, 500 μl of plasma was added to 100 μl of internal standard (itraconazole) and 125 μl of 16% ammonium hydroxide. The resulting solution was extracted with 3 ml of hexane-dichloromethane, 1:1 (vol/vol), and the organic layer was dried under nitrogen. The extract was then dissolved with 150 μl of methanol and 150 μl of 30 mM phosphate buffer (pH 5.7) and injected (100 μl) in a Waters HPLC instrument (Waters, Zellik, Belgium) equipped with a Zorbax Eclipse XDB-C18 column (Agilent, Vilvoorde, Belgium). The mobile phase was composed of the same phosphate buffer mixed with acetonitrile in a gradient ranging from 70:30 to 30:70 (vol/vol). The lower limit of quantification of the method was 200 ng/ml. At a concentration of 2,000 ng/ml, the intrarun and between-run analytical variabilities were 5.1% ($n = 4$) and 5.2% ($n = 12$), respectively.

**Data collection.** Patients' demographic, clinical and biological data were collected. Demographic and clinical data included age, sex, body mass index (BMI), type of hematological malignancy, allogeneic transplant status, comorbidities, and other ongoing treatments with proton pump inhibitors, histamine 2 (H2)-receptor antagonists, cyclosporine, or tacrolimus. The date and reason for interrupting posaconazole treatment were recorded. The presence of mucositis, diarrhea, or nausea was looked for daily and recorded according to the grades defined by the Common Toxicity Criteria for Adverse Events (CTCAE) from the European Organization for Research and Treatment of Cancer (EORTC). The presence or absence of vomiting was also checked daily and recorded in a binary way as yes or no.

The nutrition department performed a weekly evaluation of the number of calories and the quantity of food in grams ingested daily by the patients. We divided the caloric intake into three categories: >1,000 kcal/day, 500 to 1,000 kcal/day, and <500 kcal/day. A high-fat meal was defined as a meal containing more than 30 g of fat. However, when analyzing the results, we determined that no patient reached the predefined 30 g of fat intake, so we considered high-fat meals to be those containing more than 20 g of fat. Biological data collected included levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), total bilirubin, albumin, and prealbumin measured in routine blood tests.

**Statistical analysis.** Continuous data were expressed as median (range) for clinical data and median (interquartile range [Q1 to Q3]) for PPCs. Categorical data were expressed as numbers (proportions). We evaluated whether the PPCs on day $x$ were correlated with variables obtained from day $x - 1$. The prealbumin was the only variable that could be obtained up until day $x - 7$, because the variable was measured less frequently.

To take into account the repetition of dosages within the same patient, we performed a regression based on generalized estimated equation (GEE) modeling with a compound symmetry covariance matrix.

We compared PPCs at T0 and T5 using the nonparametric Wilcoxon signed-rank test for paired samples. A $P$ value of <0.05 was considered statistically significant. All the probabilities we reported are two-sided. All statistical analyses were performed by using the software SAS 9.2 (SAS Institute Inc., Cary, NC).

## RESULTS

**Patient characteristics.** A total of 40 patients were included, 32 from Institute J. Bordet and 8 from Erasme Hospital. Patients' characteristics are summarized in Table 1.

A total of 74 episodes of treatment were observed, with a median of 1 episode per patient (range, 1 to 6). The median duration of posaconazole treatment during an episode was 22 days (range, 4 to 93).

**PPC measurements.** We performed 357 PPC measurements, including 275 at T0 and 82 at T5. After inclusion of 20 patients in the study, an interim analysis revealed that there was no statistical evidence for a difference between results from T0 and T5 ($P = 0.58$). For the remaining period of the study, we measured PPCs exclusively at T0. All statistical analyses were performed with PPCs measured at T0, which are not normally distributed (Fig. 1).

**TABLE 1** Characteristics of all patients ($n = 40$)[a]

| Variable | Result[b] |
|---|---|
| Avg age (yr) | 53 (17–79) |
| BMI (kg/m$^2$) | 25 (20–36) |
| Sex (F/M) | 12/28 (30%/70%) |
| Underlying disease (AML/MDS) | 27/13 (68%/32%) |
| Allogeneic SCT | |
| Total | 11 (27%) |
| With myeloablative conditioning | 4 (10%) |
| With reduced-intensity conditioning | 7 (17%) |
| No SCT | 29 (73%) |

[a] Abbreviations: F, female; M, male; BMI, body mass index; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; SCT, stem cell transplant.
[b] The results are presented as median (range) or number (percentage).

The median number of T0 measurements per patient was 6 (range, 1 to 17). The median PPC at T0 was 430 ng/ml (Q1 to Q3, 244 to 620 ng/ml). For patients with 5 or more T0 measurements, intraindividual coefficients of variation were calculated and varied from 11% to 203% (Fig. 2).

**Clinical data.** No statistically significant relation was observed between PPC and age ($P = 0.44$), sex ($P = 0.62$), or BMI ($P = 0.12$). There was no difference in PPCs between allogeneic transplant recipients and other patients ($P = 0.33$).

Table 2 shows the influence of gastrointestinal disorders on PPC. Patients with mucositis of grade 1, 2, or 3 (median PPCs, 270 ng/ml, 280 ng/ml, and 200 ng/ml, respectively) had lower PPCs than patients without mucositis (median, 430 ng/ml; $P < 0.001$). Patients who vomited tended to have lower PPCs than those who did not vomit (230 ng/ml versus 430 ng/ml; $P = 0.05$).

Patients with a caloric intake higher than 1,000 kcal per day had significantly higher PPCs (470 ng/ml) than patients with reduced caloric intake (300 ng/ml) or no caloric intake (290 ng/ml) ($P = 0.02$). On the other hand, there was no statistical evidence that the PPCs were influenced by the fat content of the meals ($P = 0.84$) (Table 3).

**Comedications and biological data.** The concomitant use of proton pump inhibitors was associated with lower PPCs. Patients receiving proton pump inhibitors had PPCs of 390 ng/ml, compared with 510 ng/ml in patients not receiving proton pump inhibitors ($P = 0.02$). The use of either ranitidine or cyclosporine had no impact on PPCs, contrary to results with tacrolimus, which increased PPCs ($P = 0.03$) (Table 3).

There was no statistical evidence for an association between PPC and bilirubin ($P = 0.05$), ALT ($P = 0.41$), AST ($P = 0.74$), GGT ($P = 0.57$), albumin ($P = 0.97$), or prealbumin ($P = 0.07$).

**Multivariate analysis.** A multivariate analysis revealed that the variables that independently influenced PPC were the concomitant use of tacrolimus, the presence of mucositis, and the amount of caloric intake.

PPCs were on average 160 ng/ml higher in patients taking tacrolimus ($P < 0.001$).

The higher the score for mucositis, the lower the PPCs were ($P = 0.01$). Patients with a daily caloric intake of >1,000 kcal/day had an average PPC 110 ng/ml greater than the average PPC in patients with a caloric intake of 500 to 1,000 kcal/day. Patients



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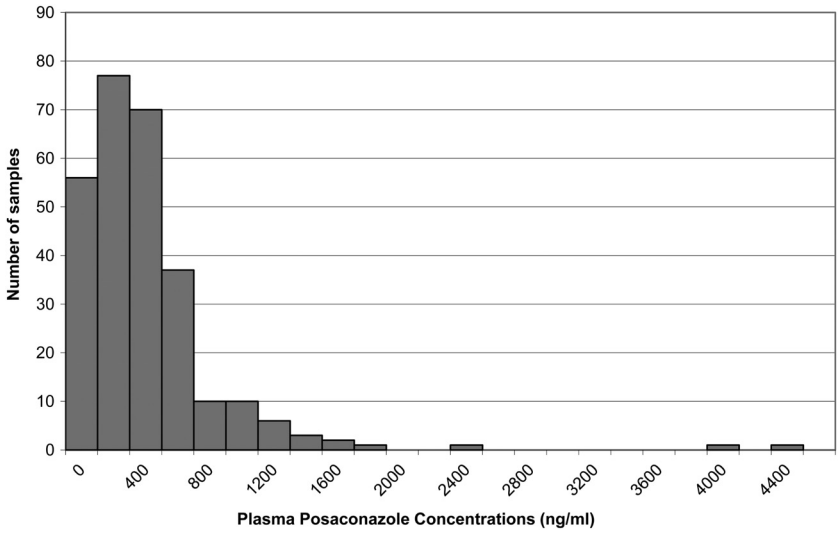


**FIG 1** Distribution of plasma posaconazole concentrations at T0.

with a daily caloric intake of 500 to 1,000 kcal/day had an average PPC 220 ng/ml greater than the average PPC in patients with a daily caloric intake of less than 500 kcal.

**Treatment discontinuation.** Seventy-four episodes of treatment were followed. Treatment was completed until neutrophil recovery in 44 of these episodes (60%). In 7 episodes (9%) treatment was interrupted for digestive intolerance with nausea and vomiting. In 2 episodes (3%), treatment was discontinued for hepatic cytolysis, and in 2 other episodes (3%), oral intake was impossible independently of digestive intolerance. One patient (1%) was transferred to another institution without treatment interruption. In 18 episodes (24%), posaconazole was shifted to another antifungal treatment either for a possible IFI (9/18), for a probable IFI (2/18), or for purely empirical treatment (7/18). PPCs observed during the 18 episodes that needed a shift to a curative antifungal treatment were significantly lower than PPCs obtained during other episodes ($P = 0.02$) (Table 4).

## DISCUSSION

Our study confirmed the high inter- and intraindividual variabilities of PPC in neutropenic patients undergoing chemotherapy for AML or MDS. The major factors influencing PPC in our patients were the severity of mucositis, the presence of digestive troubles with an impact on caloric intake, and the concomitant treatment with proton pump inhibitors or tacrolimus.

The PPC levels obtained in our study are comparable to those found in other studies with similar patient populations. The PPCs were independent of age, sex, and BMI. The median PPC in our study was 430 ng/ml (Q1 to Q3, 244 to 620 ng/ml), comparable to findings in the pharmacokinetic study by Krishna et al. on 194 neutropenic patients with AML or MDS, in which a median PPC of 486 ng/ml (range, 92 to 1,945) was obtained (12). These levels are quite low, but it has been shown that patients have lower PPCs than healthy individuals (10). Moreover, Thompson reviewed all

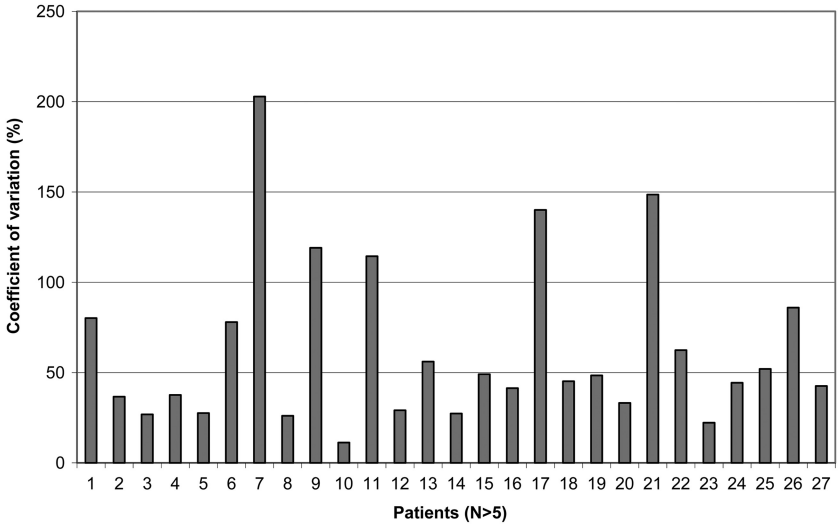


**FIG 2** Intraindividual coefficients of variation in patients with at least 5 plasma posaconazole concentration measurements.

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**TABLE 2** Influence of gastrointestinal disorders on plasma posaconazole concentration (PPC)

| Gastrointestinal condition | Grade or presence | No. of PPC measurements | Median PPC (ng/ml) | Interquartile range (Q1-Q3) | *P* value |
|---|---|---|---|---|---|
| Mucositis | 0 | 265 | 430 | 250–630 | <0.001 |
| | 1 | 6 | 270 | 200–460 | |
| | 2 | 3 | 280 | <200–300 | |
| | 3 | 1 | 200 | | |
| Nausea | 0 | 243 | 430 | 240–630 | 0.03 |
| | 1 | 14 | 600 | 400–740 | |
| | 2 | 17 | 340 | 270–450 | |
| | 3 | 1 | <200 | | |
| Vomiting | Yes | 8 | 230 | <200–360 | 0.05 |
| | No | 267 | 430 | 250–630 | |
| Diarrhea | 0 | 235 | 450 | 280–650 | 0.03 |
| | 1 | 28 | 310 | <200–480 | |
| | 2 | 8 | <200 | <200–370 | |
| | 3 | 3 | 240 | <200–360 | |
| | 4 | 1 | <200 | | |

the PPC measurements made in their laboratory and showed that 68% of PPCs were lower than 611 ng/ml (21). Our study observed that there was no significant difference between PPCs measured at T0 and T5, confirming that once the steady state is achieved, PPCs are independent of the time of sampling. This information is useful from a practical point of view, because obtaining PPCs with one blood test is simpler than obtaining PPCs with two blood tests.

**TABLE 3** Influence of food intake and comedications on plasma posaconazole concentrations

| Food parameter or comedication | No. of PPC measurements | Median PPC (ng/ml) | Interquartile range (Q1-Q3) | *P* value |
|---|---|---|---|---|
| Caloric intake | | | | |
| >1,000 kcal/day | 172 | 470 | 290–670 | 0.02 |
| 500–1,000 kcal/day | 53 | 300 | <200–480 | |
| <500 kcal/day | 5 | 290 | <200–330 | |
| Meals >20 g fat | | | | |
| Yes | 114 | 440 | 290–600 | 0.84 |
| No | 116 | 400 | 220–600 | |
| PPI[a] | | | | |
| Yes | 166 | 390 | 230–530 | 0.02 |
| No | 109 | 510 | 320–830 | |
| Ranitidine | | | | |
| Yes | 104 | 490 | 310–810 | 0.07 |
| No | 171 | 400 | 230–540 | |
| Cyclosporine | | | | |
| Yes | 25 | 430 | 290–630 | 0.07 |
| No | 250 | 430 | 240–620 | |
| Tacrolimus | | | | |
| Yes | 9 | 530 | 510–1,140 | 0.03 |
| No | 266 | 410 | 240–620 | |

[a] PPI, proton pump inhibitor.

**TABLE 4** Shift to curative antifungal treatment

| Treatment | No. of PPC measurements | Median PPC (ng/ml) | Interquartile range (Q1-Q3) | *P* value |
|---|---|---|---|---|
| No antifungal treatment | 208 | 445 | 270–670 | 0.02 |
| Curative antifungal treatment | 67 | 400 | 200–520 | |

Mucositis is a frequently observed adverse event when patients receive chemotherapy for hematological diseases. As it is rarely limited to the oral cavity, mucositis possibly interferes with the absorption of drugs. Our analysis revealed that the severity of the mucositis was significantly correlated to PPCs. These results are in agreement with a retrospective study (15) on 54 patients treated prophylactically or therapeutically with posaconazole. All patients with mucositis had low levels of posaconazole (defined as <500 ng/ml), while only 35% of those without mucositis exhibited low levels ($P = 0.004$).

In our study, PPCs were also significantly lower in patients with diarrhea, nausea, or vomiting the day preceding the PPC measurement. The lower PPC observed when the severity of diarrhea was greater was probably due to the shorter period of time posaconazole remained in the gastrointestinal tract, associated with reduced food intake. Other pharmacokinetic studies (11, 12, 13, 15) have shown similar results.

To our knowledge, our study is the first to evaluate the impact of food intake in patients treated with posaconazole and undergoing chemotherapy. Two studies in healthy volunteers showed that taking posaconazole during a meal, especially a meal rich in fat, enhanced bioavailability by 2.6 and 4 times, respectively (6, 8). High-fat meals augment posaconazole's solubility by increasing luminal volume and bile and pancreatic secretions (9). High-fat meals also delay gastric emptying. Our study confirms that even in patients undergoing chemotherapy with reduced food intake, PPCs were higher if the drug was administered with a meal; PPCs were proportional to the amount of calories ingested. However, we did not observe any correlation between fat intake and PPCs. This is not surprising, as in studies conducted in healthy volunteers (6), high-fat meals contained 50 g of fat, while in our study, not one patient was able to eat more than 30 g of fat during a meal. This resulted in a change in our definition of high-fat meals. Taking posaconazole with more than 50 g of fat per meal is not a realistic target in patients undergoing chemotherapy.

Finally, in our study, PPCs were significantly lower in patients taking concomitantly proton pump inhibitors. This effect, mediated by gastric pH, has been studied in healthy volunteers who received a single dose of posaconazole with either an acidic beverage or a proton pump inhibitor (14). The concomitant use of posaconazole and esomeprazole resulted in a decrease of the maximal concentration and of the area under the curve of 46% and 32%, respectively. Similar results were obtained with omeprazole (1). These results suggest that, whenever possible, physicians should preferentially give H2-receptor antagonists rather than proton pump inhibitors for ulcer prevention in patients taking posaconazole.



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As a CYP3A4 inhibitor, posaconazole is known to increase plasmatic concentrations of cyclosporine and tacrolimus (19, 25), but the contrary has not yet been proven. In our study, the two patients taking tacrolimus concomitantly had significantly higher PPCs than patients not taking tacrolimus. Because this effect was observed in only 2 patients, further studies are needed to confirm this effect.

Despite its prospective character, our study has limitations, including the small number of patients and the absence of standardized therapeutic optimization. In patients with low PPCs, it would be interesting to optimize posaconazole administration according to the patient's abilities: interrupt proton pump inhibitors, drink concomitantly an acidic beverage, increase caloric intake, or increase drug dose to 200 mg 4 times a day (5). However, these measures are difficult to apply to a malnourished population suffering from gastrointestinal troubles. An intravenous formulation of the drug, currently under clinical investigation, could be indicated in these patients. In the future, therapeutic drug monitoring could help to select patients who have low PPCs despite adequate drug administration and who could benefit the most from an intravenous form.

The PPC level needed to provide effective prophylaxis is still unknown. Only a few studies suggest a relationship between therapeutic response and plasmatic posaconazole levels obtained. One multicentric study on the efficacy and tolerance of posaconazole as a second-line treatment for invasive aspergillosis reported that elevated concentrations of posaconazole were associated with better clinical outcomes (24). Patients were divided in quartiles according to their PPC: the lowest PPC quartile (mean, 134 ng/ml) had a response rate of 24%, the next two quartiles had a response rate of 53%, and the highest quartile (mean, 1,250 ng/ml) had a response rate of 75%.

Optimal target drug levels for preventive therapy are not clearly established. In the retrospective review of the pharmacokinetic data of Ullmann's study on prevention in patients with allogeneic transplants, the 5 patients who developed IFI had a median PPC of 611 ng/ml (range, 158 to 1,562), compared to the other patients, who had a median PPC of 922 ng/ml (range, 0 to 3,650) (13). The retrospective review of Cornely's data on posaconazole for prevention in neutropenic patients with AML or MDS also showed that the median PPC was slightly higher in patients without IFI (median, 486 ng/ml; range, 92 to 1,945) than in the 6 patients with IFI (median, 140 ng/ml; range, 110 to 170), but these results were not statistically significant (12). In these studies there were too few cases of IFI to make clear conclusions. In our study, patients shifted from posaconazole to a curative antifungal treatment had significantly lower PPCs than the other patients. Although the shift in treatment concerned only a small number of patients and only two had probable aspergillosis, these results support the hypothesis of a dose-efficacy correlation and the interest of drug monitoring.

Given the long elimination half-life of approximately 35 h and the large apparent volume of distribution observed for posaconazole, it is likely that posaconazole concentrates and accumulates in tissues that are the site of infection at levels above those observed in the plasma. A randomized study in healthy volunteers showed higher posaconazole levels in alveolar cells (AC) than in the plasma, with an AC/plasma concentration ratio varying from 27.3 to 44.3 (3).

This could explain posaconazole's efficacy in prevention of IFI despite low PPC levels. Based on these data, authors of expert reviews propose to target a PPC of 400 to 500 ng/ml for prophylaxis and 500 to 1,500 ng/ml for treatment (2, 16).

In conclusion, our study confirmed the high inter- and intraindividual variability of posaconazole's exposition in patients treated prophylactically during chemotherapy for AML or MDS. We showed that mucositis, diarrhea, and nausea, probably by reducing the caloric intake, reduced posaconazole's bioavailability. In order to optimize the management of IFI, the optimal PPCs, as well as the exact utility of drug monitoring, still remain to be defined.

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M. Vaes is currently a research fellow with FNRS-Télévie.

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