# Comparative clinical effectiveness of prophylactic voriconazole/posaconazole to fluconazole/itraconazole in patients with acute myeloid leukemia/myelodysplastic syndrome undergoing cytotoxic chemotherapy over a 12-year period

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## ABSTRACT

Post-induction aplasia for acute myeloid leukemia/myelodysplastic syndrome is a high-risk period for invasive fungal diseases. The effectiveness of fluconazole, itraconazole solution, voriconazole and posaconazole prophylaxis used consecutively from December 1998 to January 2010 in patients with acute myeloid leukemia/ myelodysplastic syndrome undergoing remission-induction chemotherapy was retrospectively evaluated. A total of 216 consecutive patients received 573 prophylaxis courses. Breakthrough-invasive fungal disease incidence in fluconazole, itraconazole, voriconazole, posaconazole recipients was 25%, 16%, 14% and 3%, respectively. Voriconazole/posconazole *versus* fluconazole/itraconazole combined was associated with significant reductions in breakthrough-invasive fungal disease incidence (20% *vs.* 8%, $P$=0.011), premature discontinuations (46% *vs.* 22% $P$<0.001) and empiric antifungal treatment (31% *vs.* 8.5%, $P$<0.001). Microbiologically confirmed infections were molds. Posaconazole compared to other drugs was associated with fewer courses requiring computed-tomography (43% *vs.* 26%, $P$<0.001). Adoption of voriconazole/posaconazole has decreased invasive fungal disease incidence, empiric antifungal treatment and for posaconazole, computed-tomography demand, with effectiveness of posaconazole comparable to clinical trial experience.

Key words: fungal infections, prophylaxis, acute myeloid leukemia, voriconazole, posaconazole.

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## Introduction

Post-induction aplasia for acute myeloid leukemia (AML)/myelodysplastic syndromes (MDS) is a period at high-risk for invasive fungal disease (IFD).[1,2] Invasive aspergillosis (IA) remains the commonest cause of IFD and crude mortality remains considerable at 33-47%.[1,3,4] For patients surviving IFDs, delays or modifications to curative chemotherapy may compromise long-term prognosis.[2,5] Poor clinical outcomes coupled with diagnostic uncertainty underlies the rationale for antifungal prophylaxis, the efficacy of which in preventing IFD and improving short-term survival has best been demonstrated for posaconazole in AML/MDS patients receiving remission-induction chemotherapy.[6]

Despite recognition of the high health and economic burden of IFD,[7] non-selective broad-spectrum prophylaxis has raised concerns about expenditure, overtreatment and emergent drug-resistance[8] as only a subset[9] of AML patients develop IFD. Currently, a more targeted use of prophylaxis is hampered by limited knowledge of local fungal epidemiology[10] and an evolving but incomplete understanding of patient-level risk. Over ten years, we have continuously given antifungal prophylaxis in AML/MDS patients undergoing intensive chemotherapy characterized by use of fluconazole, itraconazole, voriconazole and posaconazole. We retrospectively reviewed the relative effectiveness and safety of azole antifungal prophylaxis with particular attention to the newer triazoles compared to fluconazole/itraconazole.

## Design and Methods

### Study design and setting

The Royal Melbourne Hospital is a 690-bed adult university-affiliated tertiary hospital that performs 45 allogeneic hematologic stem

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cell transplants (HSCT) annually. Consecutive patients with AML/MDS undergoing remission-induction chemotherapy from December 1998-January 2010, who received one day or more of azole prophylaxis, defining a course, were included. Prophylaxis consisting of fluconazole 400 mg daily, itraconazole solution 2.5 mg/kg bd, voriconazole 200 mg bd and posaconazole 200 mg tds co-administered with fatty food, was started at 1-2 days prior to cytoreductive chemotherapy and continued until: neutrophil recovery to more than 0.5cells/L, occurrence of a confirmed or suspected IFD, drug-related toxicity/intolerance, or the patient's condition becoming palliative. Oral administration was preferred with intravenous dosing of either fluconazole or voriconazole reserved for when gastrointestinal absorption was considered inadequate.

Suspicion of IFD lead to high-resolution computed tomography (HR-CT) introduced routinely in 2003, and lung sampling (i.e. bronochoalveolar lavage/biopsy) as tolerated. Galactomannan (GM) or beta-D-glucan assays were not used. AML treatment protocols were predominantly anthracycline and cytarabine based. Neutropenic fever was treated with cefepime prior to 2005 and piperacillin-tazobactam thereafter. Empiric antifungal therapy (EAFT), usually liposomal amphotericin, was typically initiated, once voriconazole and posaconazole prophylaxis became routine, in the presence of HR-CT changes suspicious for IFD. G-CSF was used as part of trial protocols or at the physician's discretion when expected neutropenia duration was 18-days or over. The majority of patients received proton-pump inhibitors for stress ulcer prophylaxis. Therapeutic drug monitoring (TDM) was not routine.

High efficiency particulate air-filtration (HEPA) was extended from five to all rooms in April 2005. However, the vast majority of patients were nursed in HEPA-filtered rooms from 1996-2005.

### Clinical data, definitions and imaging review

Collected information included host and treatment-related characteristics, receipt of total parenteral nutrition (TPN) as a surrogate marker of severe mucositis and chest/sinus CT scans performed 3-days prior to, during prophylaxis or within seven days from drug cessation. IFD classification adhered to consensus criteria[11] whereby probable/proven cases required fungal pathogen isolation. IFD onset was defined as the first day of suspicious CT abnormality or positive microbiology or pathological test. CT scans were reviewed by a radiologist (JV) blinded to IFD classification, for the presence of accepted IFD-related lesions[11] as distinct from non-specific pulmonary infiltrates.

Prophylactic effectiveness was assessed in patients receiving azoles at standard doses for 7 consecutive days or more (to approximate steady-state). Breakthrough-IFD was defined as occurrence of IFD in patients during azole prophylaxis or seven days or less from drug cessation. Antifungal susceptibility testing of fungal isolates followed reference methods.[12]

Plasma concentrations of itraconazole, voriconazole and posaconazole drawn five days or more after drug commencement (to approximate steady-state) were defined as sub-therapeutic for: itraconazole 0.5 μg/mL or less; voriconazole less than 0.7mg/L and posaconazole less than 500ng/L.[13] Institutional ethics approval was obtained.

### Statistical analysis

The primary objective of the study was to evaluate the incidence of breakthrough-IFD. Secondary outcomes were requirement for EAFT and toxicity/ tolerability. Prophylaxis courses in patients who either died or became palliative were excluded from safety analyses. Categorical variables were analyzed using the $\chi^2$ test or Fisher's exact test as appropriate. The Student's t-test or Wilcoxon's rank-sum test was used to compare continuous variables depending on their distribution. Differences in continuous variables between the azole drugs were assessed using the Kruskal-Wallis test. Reported *P* values were two-tailed and for each analysis $P \leq 0.05$ was considered significant. All analyses used Stata 11.0 software (Stata Corp, College Station, Texas, USA).

## Results and Discussion

### Patients' characteristics according to azole antifungal prophylaxis

A total of 216 patients (91% with AML) received 573 courses of azole prophylaxis (Table 1). The majority of patients (213 of 216, 99%) underwent chemotherapy for remission-induction/re-induction or relapsed disease. Significant differences in clinical characteristics were noted between fluconazole/itraconazole and voriconazole/posaconazole recipients, respectively: median duration of neutropenia per prophylaxis course [16-days *vs.* 14-days, $P=0.003$], median age (56 *vs.* 51-years, $P<0.001$), male gender (47% *vs.* 56%, $P=0.035$), TPN requirement (39% *vs.* 26%, $P=0.001$) and median duration of prophylaxis (18 days *vs.* 22 days, $P<0.001$). Changes in clinical practice may have accounted for some of these differences. For example, fluconazole early in the study period was started during chemotherapy or at its cessation accounting for its shorter duration of use, a practice that was later abandoned due to the high number of breakthrough-IFDs.

### Breakthrough-IFDs

Breakthrough-IFDs occurred in 27 patients (27 of 216, 13%) comprising probable/proven (n=11) and possible (n=16) infections (Table 2). Among the 210 patients who received seven days or more of azole prophylaxis, breakthrough probable/proven-IFD incidence declined over time: fluconazole 6 of 36, 17%; itraconazole 4 of 49, 8.2%; voriconazole one of 58, 1.7%; posaconazole 0 of 67 with a similar trend following inclusion of possible-IFDs: 9 of 36, 25%; 8 of 49, 16%; 8 of 58, 14% and 2 of 67, 3.0% respectively. The incidence of breakthrough possible/probable/proven-IFDs associated with voriconazole/posaconazole was significantly lower than fluconazole/ itraconazole (17 of 85, 20% *vs.* 10 of 125, 8.0%, $P=0.011$).

All probable/proven IFDs were molds, most commonly aspergillosis. The single *A. fumigatius* isolate tested for susceptibility (2001) demonstrated reduced dose-dependent susceptibility to itraconazole in a patient who had consecutive courses of itraconazole prophylaxis lasting 23 and 15 days, 18 days apart and later died of *Aspergillus* pneumonia. IFD complicated remission-induction chemotherapy in 24 of 27 patients (9 of 24 had disease relapse) and consolidation chemotherapy in 3 patients. Breakthrough probable/proven-IFD incidence among patients receiving one day or more of prophylaxis (similar to an intention-to-treat group), with occurrence during or 30 days or less from drug cessation, was: fluconazole 8 of 57, 11%; itraconazole 6 of 59, 10%; voriconazole 2 of 82, 2.4%; and posaconazole 0 of 68.

### Plasma levels of itraconazole, voriconazole and posaconazole

A total of 55 patients had 141 plasma levels after five days or more of itraconazole, voriconazole or posacona-

zole. Sub-therapeutic plasma drug levels, regardless of timing (i.e. trough, peak, random), were common for itraconazole (15 of 36, 42%), voriconazole (35 of 92, 38%) and posaconazole (9 of 13, 69%). None of the 5 patients with breakthrough probable/proven-IFDs during itraconazole or voriconazole prophylaxis had TDM performed. There was no significant difference in median drug levels with or without TPN (administered in the seven days prior to plasma level) (*data not shown*).

### Discontinuations, use of empiric antifungal therapy and CT scan demand

Table 3 describes secondary outcomes analyzed according to course of prophylaxis. Overall, premature discontinuations, for any reason, were significantly higher among fluconazole/itraconazole compared to the voriconazole/posaconazole groups combined (46% *vs.* 22%, *P*<0.001). Escalation to EAFT lasting four days or more accounted for the majority of fluconazole and itraconazole discontinuations (74% and 62%, respectively) and to a lesser extent voriconazole (51%). Gastrointestinal-related discontinuation rates were similar for itraconazole and posaconazole (19% each) but accounted for the majority of premature discontinuations for posaconazole (71%) compared to 42% for itraconazole. This was not due to differences in severe mucositis reflected by TPN requirement (71% *vs.* 76%, respectively). Hepatotoxicity was low overall but significantly higher for voriconazole compared to the other drugs combined (5% *vs.* 1.1%, *P*=0.007).

EAFT was higher in the combined fluconazole/itraconazole compared to the voriconazole/ posaconazole groups (31% *vs.* 8.5%, *P*<0.001) as were pulmonary lesions on computed-tomography treated for suspected IFD but not meeting criteria for possible-IFD (10% *vs.* 4.0%, *P*=0.004). Itraconazole offered no advantage over voriconazole/posaconazole in preventing pulmonary lesions consistent with IFD (8.7% *vs.* 4.0%, *P*=0.047). Demand for CT scans was not diminished with voriconazole/posaconazole compared to fluconazole/itraconazole (42% *vs.* 37%, *P*=0.26) due to the high numbers of voriconazole courses necessitating CT scanning (45%); only posaconazole was associated with a significant reduction compared to fluconazole/itraconazole/voriconazole courses combined (43% *vs.* 26%, *P*<0.001).

**Table 1.** Clinical characteristics according to azole antifungal prophylaxis.

| Characteristic | Fluconazole n (%) | Itraconazole n (%) | Voriconazole n (%) | Posaconazole n (%) |
|---|---|---|---|---|
| Characteristics of patients, n=216 | | | | |
| N. of patients[1] | 57 | 59 | 82 | 68 |
| Age at start of chemotherapy, years | | | | |
| Median, range | 57, 20-79 | 55, 20-79 | 51, 17-81 | 51, 19-78 |
| Male gender | 27 (47) | 29 (49) | 38 (46) | 43 (71) |
| Dates of use | Dec 1998-Sept 2008 | May 1999-Jan 2003 | Nov 2002-Aug 2008 | Sept 2006-Jan 2010 |
| Characteristics per prophylaxis course, n=573 | | | | |
| N. of prophylaxis courses | 95 (17) | 119 (21) | 206 (36) | 153 (27) |
| Underlying diagnosis | | | | |
| AML[2] (197 patients) | 73 (77) | 112 (94) | 195 (95) | 145 (95) |
| Transformed MDS (18 patients) | 22 (23) | 7 (5.9) | 11 (5.3) | 8 (5.2) |
| Phase of treatment | | | | |
| Induction/re-induction | 55 (58) | 63 (53) | 83 (43) | 67 (44) |
| Relapse | 10 (11) | 16 (13) | 26 (13) | 15 (9.8) |
| Consolidation | 30 (32) | 40 (34) | 97 (47) | 71 (46) |
| Duration of neutropenia (≤0.5 cells/L) per chemotherapy cycle, days | | | | |
| Median, range | 16, 0-54 | 16, 4-41 | 13, 0-54 | 15, 0-48 |
| Receipt of TPN, n (%) | 36/95 (38) | 48/119 (40) | 44/206 (21) | 48/153 (31) |
| Duration of prophylaxis, days | | | | |
| Median, range | 15, 3-53 | 20, 1-71 | 21, 2-79 | 23, 1-69 |

*[1]Some patients received more than one antifungal drug as prophylaxis; [2]includes one patient with acute undifferentiated leukemia who received 4 courses of posaconazole prophylaxis.*

**Table 2.** Clinical characteristics of patients with breakthrough invasive fungal disease.

| Characteristic | Fluconazole | Itraconazole | Voriconazole | Posaconazole |
|---|---|---|---|---|
| Probable or proven IFDs[1] | 6 | 4 | 1 | 0 |
| Female sex | 4 | 1 | 1 | NA |
| Age, years Median (range) | 50 (40-60) | 59.5 (50-70) | 71 | NA |
| Year of IFD diagnosis | 1999, 2000, 2003/04 | 2001/02 | 2003 | NA |
| Underlying disease | AML | AML | AML | NA |
| Phase of treatment | | | | NA |
| Induction/re-induction | 5 | 3 | 0 | |
| Induction for relapse | 1 | 0 | 1 | |
| Consolidation | 0 | 1 | 0 | |
| Site of infection | | | | NA |
| Lung | 5 | 3 | 1 | |
| Sinus | 1 | 0 | 0 | |
| Blood | 0 | 1 | 0 | |
| Organism | | | | NA |
| *A.fumigatus* | 2 | 1 | 0 | |
| *A. niger* | 1 | 0 | 0 | |
| Fungal hyphae resembling *Aspergillus spp.* | 2 | 1 | 0 | |
| Fungal hyphae not specified | 0 | 1 | 0 | |
| *Rhizopus spp.* | 1 | 0 | 1 | |
| *Scedosporium prolificans* | 0 | 1 | 0 | |
| Receipt of TPN[2] | 4/6 | 3/4 | 0/1 | NA |
| Outcome at 12 weeks | | | | NA |
| Cure | 3 | 0 | 0 | |
| Unfavorable response[3] | 3 | 4 | 1 | |
| Death | 3 | 2 | 0 | |
| Possible IFD[4] | 3 | 4 | 7 | 2 |
| Lung resection performed | 0 | 2 | 1 | 2 |
| Lung biopsy or lavage | 2 | 4 | 1 | 2 |
| Any positive PCR | 0/1 | 1/2 | 0/1 | 0/2 |
| Probable or proven IFDs by intention-to-treat[5] | 8 | 6 | 2 | 0 |

*IFD: invasive fungal disease; AML: acute myeloid leukemia; TPN: total parenteral nutrition; [1]IFD occurrence in patients receiving ≥7 days of antifungal prophylaxis, during or ≤7 days from cessation of azole prophylaxis; [2]Receipt of TPN a surrogate marker for the presence of mucositis; [3]Unfavorable response defined as partial response, progressive infection or death; [4]Evidence of either halo, nodule(s) or cavitation on computed tomography of the chest. Non-specific pulmonary infiltrates or infiltrates not suggestive of fungal infection were excluded; [5]IFD occurrence during or ≤30-days of drug cessation in patients receiving ≥1-days of prophylaxis.*

## Discussion

In our center, adoption of voriconazole/posaconazole in comparison to fluconazole/itraconazole prophylaxis in a high-risk cohort of AML/MDS patients was associated with a significant decrease in the incidence of breakthrough possible/probable/proven-IFD (20% *vs.* 8.0%, *P*=0.011) in addition to reductions in less specific but not insignificant outcomes including escalation to EAFT (31% *vs.* 8.5%, *P*<0.001) and pulmonary lesions on computed-tomography treated for suspected IFD but not meeting consensus criteria for possible-IFD[11] (10% *vs.* 4.0%, *P*=0.004). A declining trend in breakthrough proven/probable-IFDs (fluconazole 17%, itraconazole 8.2%, voriconazole 1.7%) persisted when more stringent criteria similar to an intention-to-treat analysis were applied (fluconazole 11%, itraconazole 10%, voriconazole 2.4%). Notably, the breakthrough-IFD incidence of 3% associated with posaconazole was due to possible IFDs and comparable to the 2% proven/probable-IFD incidence in the randomized trial.[6] Qualifying these findings is the fact that as a non-contemporaneous cohort, host or treatment-related factors (e.g. duration of azole prophylaxis or neutropenia) may have contributed to improvements in effectiveness but further analysis controlling for key variables was not possible due to low numbers of breakthrough-IFDs overall.

Local epidemiology informs the choice and risk-benefit of prophylaxis. Prophylaxis seems warranted in our setting where baseline IFD incidence is likely higher than the 17% observed in our fluconazole cohort, and above the 15% threshold identified in a meta-analysis of non-HSCT neutropenic patients.[14] In our setting, the number-needed-to-treat (NNT) with posaconazole prophylaxis to prevent one probable/proven IFD is 6, which is lower than the posaconazole registration trial (NNT=16)[15] but similar to other real-world experience comparing posaconazole to topical polyene prophylaxis (NNT=7).[10] Breakthrough-IFDs were predominantly IA, in keeping with the decline in invasive candidiasis seen in recent years,[16] but notable in our setting given the high requirement for TPN and its association with mucositis, both of which are risk factors for invasive candidiasis.[17]

Premature discontinuations were lower with voriconazole/posaconazole compared to fluconazole/itraconazole (46% *vs.* 22%, *P*<0.001). Clinical failure denoted by escalation to EAFT accounted for the majority of discontinuations among the standard azoles (fluconazole 74%, itraconazole 62%). Concern regarding potential incomplete gastrointestinal absorption or intolerance accounted for the majority of posaconazole discontinuations (71%) compared to 42% for itraconazole. This was likely due to a greater propensity for gastrointestinal intolerance with itraconazole and the lack of an iv formulation for posaconazole when mucositis supervened. The Cologne group,[10] in contrast, reported no significant intolerance/toxicities associated with posaconazole, perhaps reflecting a higher degree of clinician confidence in the drug even in the presence of mucositis. Serious adverse events were consistent with the recognized toxicities of azoles[18] but for voriconazole, less frequent than post-marketing reports.[19,20]

The emergence of resistant fungi is a potential drawback of broad-spectrum antifungal prophylaxis. Intrinsically resistant organisms including *A. niger*, *Scedosporium prolificans* and *Rhizopus spp*. were seen but in association with fluconazole, itraconazole, and both fluconazole/voriconazole, respectively, limiting conclusions about causation. Our single case of possible acquired itraconazole resistance echoes the low prevalence of azole resistance in *Aspergillus* isolates (0.85%) reported from a hematology unit where periods of drug exposure were also short.[21]

TDM was performed when absorption was suspected to be inadequate. Therefore, subtherapeutic levels were common and further interpretation was limited by an absence of TDM among the 5 patients who developed probable/proven IFDs.

Our burden of IFD is likely underestimated due to a lack of routine GM testing and, like other transplant centers, falling autopsy rates. Multiple prophylactic azole drugs

**Table 3.** Reasons for discontinuation of azole prophylaxis courses.[1]

| Clinical outcome | Fluconazole, n (%) | Itraconazole, n (%) | Voriconazole, n (%) | Posaconazole, n (%) | *P*[2] |
|---|---|---|---|---|---|
| Premature discontinuation, n. of courses (%)[1] | 42/93 (45) | 53/115 (46) | 37/202 (18) | 41/149 (28) | <0.001[3] |
| Reason for discontinuation: | | | | | |
| EAFT (≥4days) for suspected IFD | 31/93 (33) | 33/115 (29) | 19/202 (9.4) | 11/149 (7.4) | <0.001[3] |
| EAFT & pulmonary lesions suggestive of IFD[4] | 11/93 (12) | 10/115 (8.7) | 9/202 (4.5) | 5/149 (3.4) | <0.001[3] |
| Gastrointestinal intolerance/absorption concerns | 2/93 (2.2) | 22/115 (19) | 7/202 (3.5) | 29/149 (19) | 0.012[5] |
| Receipt of TPN in subset with GIT absorption/intolerance concerns | 0/2 | 16/22 (73) | 4/7 (57) | 22/29 (76) | * |
| Abnormal LFTs[6] | 1/93 (1.1) | 2/115 (1.7) | 10/202 (5) | 1/149 (0.7) | 0.009[7] |
| Other[8] | 4/93 (4.3) | 3/115 (2.6) | 4/202 (2.0) | 1/149 (0.7) | * |
| Courses discontinued due to death[2] or palliation of patient | 2 | 4 | 4 | * | |

*EAFT: empiric antifungal treatment; TPN: total parenteral nutrition; LFTs: liver function tests; IFD: invasive fungal disease. [1]In some cases patients discontinued drugs for more than one reason. Premature discontinuation excludes courses where patients subsequently died or were palliated; [2]test of difference used the $\chi^2$ test or Fisher's exact test as appropriate; [3]comparing discontinuation in the standard azole (fluconazole, itraconazole) vs. voriconazole+posaconazole groups combined; [4]Pulmonary lesions treated for suspected invasive fungal infection but not meeting consensus criteria.[11] [5]Comparing discontinuation in the itraconazole vs. voriconazole+posaconazole groups combined. [6]Abnormal LFTs according to clinician judgment as documented in medical chart. [7]Comparing discontinuation in voriconazole vs. fluconazole/itraconazole/posaconazole groups combined. [8]Includes discontinuations due to photopsia and rash (voriconazole, n=2); avoidance of drug-drug interactions with voriconazole (all-trans retinoic acid and arsenic in one patient and amiodarone in another patient); ventricular fibrillation associated with a prolonged QT interval with posaconazole (n=1); reasons for discontinuation were unclear for fluconazole and itraconazole. *No test of comparison performed.*

were administered to 52 patients (*data not shown*) during their entire treatment schedule due to toxicities/intolerance, changes in unit policy, or following long intervals between treatment, e.g. disease relapse. Therefore, we analyzed courses rather than patients assuming that episodes of chemotherapy-induced neutropenia were discrete, temporally separate and, therefore, independent periods of risk. The choice of fluconazole/itraconazole as comparators to voriconazole/posaconazole was based on clinical trial experience.[6] That consolidation chemotherapy is low risk for IFD (affecting 3 of 27 patients) compared to post-induction aplasia[1,16,22] suggests review of our universal policy of broad-spectrum prophylaxis may be warranted.

Concordance of real-world effectiveness of posaconazole prophylaxis with trial experience is reassuring but we welcome advances in risk-stratification tools to better direct prophylaxis to those at highest risk. However, unless persuasive evidence emerges that approaches alternative to broad-spectrum prophylaxis[23] do not threaten longer term outcomes, i.e. the completion and intensity of leukemia treatment, due to the development of IFD,[5] then it is not a strategy we are likely to abandon but would prefer to refine.

## Authorship and Disclosures

*The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.*

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