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Pharmacoeconomic evaluation of fluconazole, posaconazole and voriconazole for antifungal prophylaxis in patients with acute myeloid leukaemia undergoing first consolidation chemotherapy

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Background: Fluconazole, posaconazole and voriconazole are used prophylactically in patients with acute myeloid leukaemia (AML). This study evaluated the clinical and economic outcomes of these agents when used in AML patients undergoing consolidation chemotherapy.

Methods: A retrospective chart review (2003–10) of AML patients receiving consolidation chemotherapy was performed. Patients were followed through their first cycle of consolidation chemotherapy. Antifungal prescribing patterns, clinical outcomes and resource consumptions were recorded. A decision analytical model was developed to depict the downstream consequences of using each antifungal agent, with success defined as completion of the designated course of initial antifungal prophylaxis without developing invasive fungal disease (IFD). Cost-effectiveness and sensitivity analyses were performed.

Results: A total of 106 consecutive patients were analysed. Baseline characteristics and predisposing factors for IFD were comparable between groups. Three IFDs (one proven, one probable and one suspected) occurred, all in the posaconazole group. Patients receiving posaconazole had the highest rate of intolerance requiring drug cessation (13% versus 7% in each of the fluconazole and voriconazole groups). Fluconazole conferred overall savings per patient of 26% over posaconazole and 13% over voriconazole. Monte Carlo simulation demonstrated a mean cost saving with fluconazole of AU$8430 per patient (95% CI AU$5803–AU$11 054) versus posaconazole and AU$3681 per patient (95% CI AU$990–AU$6319) versus voriconazole. One-way sensitivity analyses confirmed the robustness of the model.

Conclusions: This is the first study to show that, in the setting of consolidation therapy for AML, fluconazole is the most cost-effective approach to antifungal prophylaxis compared with posaconazole or voriconazole.

Keywords: antifungals, AML, modelling

Introduction

Patients receiving myelosuppressive chemotherapy for acute myeloid leukaemia (AML) are vulnerable to invasive fungal diseases (IFDs), with the reported rate of mould infections (predominantly *Aspergillus* species) of the order of 7.9% and yeast infections around 4.4%.[1] The mortality rate of IFD is substantial[2,3] as the response to antifungal treatment is often poor[4,5] and the cost of treating IFD is high.[6] Accordingly, there has been a focus on using antifungal prophylaxis in patients

with haematological malignancies, whereby a number of antifungal agents, including fluconazole,[7] voriconazole[8–10] and posaconazole,[11] are used. The results of these studies have led to antifungal prophylaxis being strongly recommended[12–14] during the high-risk period of prolonged post-induction aplasia.[1,15]

To date, only fluconazole and posaconazole have shown a survival benefit when used prophylactically in the haematology population.[11,16] Fluconazole lacks activity against moulds (e.g. *Aspergillus*) and *Candida krusei*,[17] whereas posaconazole provides broad-spectrum coverage. Voriconazole, another broad-spectrum antifungal agent, was commonly used prior to the availability of posaconazole,[9,10] but evidence from clinical trials for its prophylactic effectiveness in AML is lacking. Whilst the randomized trial by Cornely *et al*.[11] showed superiority of posaconazole prophylaxis over fluconazole/itraconazole in decreasing IFD during induction chemotherapy, translation of the benefit into consolidation cycles remains unknown.[14,16]

Most studies have focused on the clinical efficacy and cost-effectiveness of prophylaxis during induction chemotherapy of AML or myelodysplastic syndrome.[7,8,11,18–23] There is little evidence, however, to guide the appropriate use of antifungal prophylaxis in patients with AML undergoing consolidation chemotherapy,[24] where the risk for IFD is lower than during induction.[25,26] It is unknown if the benefit of antifungal prophylaxis during consolidation chemotherapy with posaconazole or voriconazole outweighs their higher drug acquisition costs compared with fluconazole.

Accordingly, we investigated the clinical and economic outcomes of fluconazole, posaconazole and voriconazole in AML patients undergoing the first consolidation chemotherapy cycle after successful induction.

Methods

Perspective

The economic modelling was conducted from the Australian public hospital perspective, encompassing costs incurred from index admission for administration of consolidation chemotherapy cycle 1 through to the day prior to commencement of consolidation chemotherapy cycle 2, or the end of the assessment period at day 40, whichever was earlier. This costing period, which covered the at-risk period for IFD in consolidation chemotherapy cycle 1, included subsequent elective re-admission(s) and outpatient stay(s) between admissions. Only direct medical costs related to the management of IFD were accounted for. Given that the focus of the study was on prophylactic antifungal therapy, costs of underlying conditions were not included. Indirect and non-medical costs were also excluded as the patients' social and employment data were not readily available.

Model structure

A decision analytical model involving four possible treatment pathways was constructed to depict the downstream consequences of initial antifungal prophylaxis with fluconazole, posaconazole or voriconazole in patients with AML undergoing consolidation chemotherapy cycle 1 (Figure 1). Success was defined as completion of the designated full course of initial antifungal prophylaxis without breakthrough IFD. Failure was defined as the premature discontinuation of initial prophylaxis and switching to alternative therapy due to any of the following reasons: (i) proven, probable or possible breakthrough IFD, as defined by the European Organisation for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG),[27] or empirical use of systemic antifungal treatment for clinically suspected IFD, or (ii) intolerance due to poor oral intake or gastrointestinal intolerance (e.g. diarrhoea, vomiting) or any other conditions that raised concern about oral absorption of the antifungal agent. Patients who failed prophylaxis due to documented or suspected IFD were switched to targeted or empirical antifungal treatment and followed until therapeutic success (defined as cessation of antifungal treatment without progression of IFD) or death. The death pathway refers to overall mortality, given the difficulties in attributing the cause of death to IFD ante-mortem[28,29] and the occult effect of drug-related adverse events on survival. Patients who failed initial prophylaxis because of intolerance and switched to alternative prophylactic antifungals were followed until the end of the assessment period.

Model inputs

This study was approved by the human ethics committees of Melbourne Health, Peter MacCallum Cancer Centre and Monash University. Clinical and resource consumption data used to populate the model were extracted from a 6 year retrospective review of medical records (November 2003 to January 2010) of all patients with AML admitted for consolidation chemotherapy cycle 1 at the Royal Melbourne Hospital and the Peter MacCallum Cancer Centre. Both tertiary hospitals have comparable standards and levels of patient care, including treatment protocols for haematological malignancies and diagnostic procedures. In addition, two infectious diseases physicians (M. S. and K. T.) provide consultation at both hospitals.

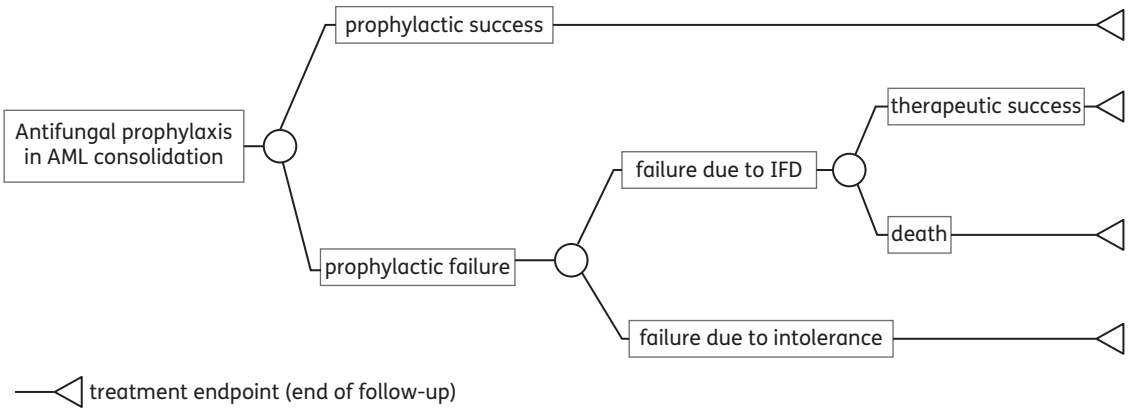

Figure 1. Decision analytical model of antifungal prophylaxis in AML consolidation chemotherapy.

Adult patients aged ≥18 with AML in complete remission after induction chemotherapy were included in the study if they received fluconazole, posaconazole or voriconazole as the initial antifungal prophylaxis during their first consolidation chemotherapy. Doses of fluconazole (orally, 200 mg daily), posaconazole (orally, 200 mg three times daily) and voriconazole (orally, 400 mg twice daily on day 1 and then 200 mg twice daily) were prescribed according to the Australasian antifungal guidelines.[30] Oral prophylactic antifungals were commenced at the beginning of the index admission. Patients receiving systemic antifungals for empirical treatment of suspected IFD within 7 days prior to initiation of fluconazole, posaconazole or voriconazole prophylaxis in the consolidation stage, those with active or previous diagnosis of proven or probable IFD, baseline renal impairment [creatinine level ≥2 times the upper limit of normal (ULN)] or baseline hepatic insufficiency (any liver function test ≥2 times the ULN) were excluded. Baseline characteristics between the three groups were compared by the Kruskal–Wallis test for continuous variables and the χ^2 test for categorical variables, using SPSS version 17.0 (IBM SPSS, Inc.).

Cost calculations

The cost of prophylaxis success included the drug acquisition costs of initial prophylaxis with fluconazole, posaconazole or voriconazole, inpatient stay, outpatient clinic visit and relevant resources consumed throughout hospitalization and outpatient stay [i.e. monitoring (e.g. full blood count, renal and liver function tests) and diagnostic (e.g. chest X-ray or CT scan, histopathological examination, microscopy and cultures) tests and diagnostic procedures (e.g. bronchoscopy with bronchoalveolar lavage, tissue biopsy and lumbar puncture)]. The cost of prophylactic failure included costs of items as listed for the cost of prophylaxis success and, where applicable, the costs of alternative prophylaxis, empirical or targeted antifungal therapy.

All costs were expressed in Australian dollars (AU$) for the financial year 2011/12. Discounting was not applied because no adjustment of future cost to the present was required. Medication acquisition costs were obtained from Health Purchasing Victoria (HPV) tender 2010–12,[31] which represents the drug wholesale prices paid by public hospitals in the state of Victoria, or from the public hospital procurement system for medications (voriconazole and posaconazole) that are not in the HPV list. Drug acquisition costs were calculated based on actual doses administered to patients. The cost of hospitalization, specifically for the acute leukaemia patient group, was obtained from the Australian Refined Diagnosis Related Group (AR-DRG) 2009–10[32] and inflated to the financial year 2011/12 according to the Australian Health Consumer Price Index 2012.[33] The costs of pathology, pharmacy, imaging and critical care were excluded from the hospitalization cost obtained from the AR-DRG to avoid double counting. The costs of monitoring and diagnostic tests, diagnostic procedures and outpatient clinic visits were based on the Australian Medicare Benefits Schedule Book 2012.[34] The costs of resources used are listed in Table 1.

Table 1. Resource costs

Item	Unit	Cost (AU$)
Fluconazole	200 mg oral capsule	2.34
Posaconazole	105 mL/bottle oral suspension	659.75
Voriconazole	200 mg oral tablet	45.15
	200 mg iv vial	187.07
Liposomal amphotericin B	50 mg iv vial	295.00
Terbinafine	250 mg oral tablet	0.47
Chest X-ray	1 test	35.35
CT scan	1 test	295.00
Ultrasound scan	1 test	111.30
MRI scan	1 test	403.20
Blood C&S	1 test	30.95
Urine C&S	1 test	20.70
Non-blood C&S[a]	1 test	48.45
Bronchoscopy/BAL	1 test	252.15
Lung biopsy	1 test	121.50
Skin biopsy	1 test	51.25
Lung wedge resection	1 test	1125.80
Lumbar puncture	1 test	71.15
PCR	1 test	28.85
Serology	1 test	49.00
Histology	1 test	72.00
Full blood count	1 test	17.05
Renal function test	1 test	155.40
Liver function test	1 test	17.80
Outpatient clinic visit	1 follow-up	74.10
Hospitalization	general ward per day	1177.00

MRI, magnetic resonance imaging; C&S, culture and susceptibility; BAL, bronchoalveolar lavage.
[a]Non-blood culture includes specimens from wound swab, biopsies, CSF, bronchoalveolar lavage fluid, pleural fluid, catheter tip, sputum and skin.

Sensitivity analyses

The robustness of model outcomes to variation in the values of key variables and alternative scenarios was evaluated using deterministic and probabilistic sensitivity analyses. An alternative scenario was used to analyse the impact of matching the three groups according to age (<60 versus ≥60 years old), as described in our previous study,[20] as advanced age is associated with less favourable response to chemotherapy and predisposes patients to a higher risk of IFD.[35] In another scenario, three patients with IFD were excluded from the posaconazole cohort to account for possible imbalance in the number of IFDs between groups due to small sample size.

The effects of variation in cost estimates and key parameters of the model, such as acquisition costs of antifungal drugs, hospitalization cost, daily dose of fluconazole (400 mg versus 200 mg) and the use of monitoring and diagnostic tests, were investigated using one-way sensitivity analyses. Variation ranges of the key variables are detailed in Table 2. Threshold analyses were performed by varying the total average durations of hospitalization of each fluconazole, posaconazole and voriconazole group until the model conclusion changed.

Monte Carlo probabilistic sensitivity analysis was conducted using @Risk 5.5® software (Palisade Corporation, Ithaca, NY, USA). The uncertainty ranges of the model inputs (i.e. outcome probabilities) were predefined by triangular distribution at ±10%. A total of 10000 simulations were performed. Corresponding costs were calculated and the probability of cost saving was evaluated using a distribution curve. The impact of input parameters on the overall costs was determined.

Results

Clinical outcomes

One hundred and six patients receiving consolidation chemotherapy cycle 1 were evaluated (fluconazole, $n=30$; posaconazole, $n=47$; voriconazole, $n=29$). Patients in the fluconazole and posaconazole groups were recruited between 2005 and

Table 2. Variation range for key variables in sensitivity analysis

Variable	Base case	Variation range	
		low	high
Fluconazole cost/capsule, AUD$	2.34	1.17	3.51
Posaconazole cost/bottle, AUD$	659.75	329.88	989.63
Voriconazole cost/tablet, AUD$	45.15	22.57	67.73
Liposomal amphotericin B cost/vial, AUD$	295.00	147.50	442.50
Hospitalization cost/day, AUD$	1177.00	588.50	1765.50
Daily dose of fluconazole	200 mg	200 mg	400 mg
Duration of hospitalization (fluconazole), days	17	17	24
Duration of hospitalization (posaconazole), days	19	12	19
Duration of hospitalization (voriconazole), days	17	14	17
Counting for costs of monitoring, pathology and imaging tests, and outpatient follow-up	yes	no	yes

Table 3. Baseline demographic and clinical characteristics of patients

Characteristic	Fluconazole ($n=30$)	Posaconazole ($n=47$)	Voriconazole ($n=29$)
Age			
years, median (range)	62 (17–75)	55 (23–79)	54 (18–77)
<60 years, *n* (%)	13 (43.3)	29 (61.7)	19 (65.5)
≥60 years, *n* (%)	17 (56.6)	18 (38.3)	10 (34.5)
Male sex, *n* (%)	18 (60.0)	26 (55.3)	16 (55.2)
Weight (kg), median (range)[a]	76.8 (43–130)	72.0 (40–116)	73.0 (49–107)
Previous induction cycles, *n* (%)			
1	29 (96.7)	40 (85.1)	28 (96.6)
2	1 (3.3)	7 (14.9)	1 (3.4)
Prophylaxis used in previous induction cycles, *n* (%)[b]			
voriconazole	12 (40.0)	3 (6.1)	29 (100.0)
posaconazole	16 (53.3)	45 (95.7)	2 (6.9)
fluconazole	3 (10.0)	3 (6.1)	2 (6.9)
liposomal amphotericin B	1 (3.3)	13 (26.5)	5 (17.2)
intermediate- to high-dose chemotherapy, *n* (%)	10 (33.3)	15 (31.9)	12 (41.4)
dose of cytarabine: g/m^2/day; median (range)	0.1 (0.1–3)	0.3 (0.1–6)[c]	0.3 (0.1–4)
Neutropenia, *n* (%)	29 (96.7)	46 (97.9)	29 (100.0)
total duration (days), median (range)[d]	7.5 (3–52)	6.5 (3–50)	6.0 (3–29)
Total length of hospitalization (days), median (range)	17 (5–40)	19 (5–42)	17 (5–34)

$P>0.05$ for all comparisons (by Kruskal–Wallis test for continuous variables and χ^2 test for categorical variables).
[a]Missing data for three patients (one in the posaconazole group and two in the fluconazole group).
[b]Some patients had switching in antifungal prophylactic agent.
[c]One patient received a chemotherapy regimen without cytarabine.
[d]Total duration of grade 4 neutropenia (absolute neutrophil count $<0.5\times10^9$/L) at any point during the 40 day assessment period. The neutropenia duration for three patients in the voriconazole group and one patient in the posaconazole group was a composite of two single neutropenic episodes.

2010, whereas those receiving voriconazole were recruited between 2003 and 2008. The demographics of each group are summarized in Table 3. All groups had similar baseline characteristics and predisposing factors for IFD, including intensity of chemotherapy regimens (intermediate- to high-dose cytarabine, ≥1.5 g/m^2) ($P=0.69$), duration of grade 4 neutropenia (absolute neutrophil count $<0.5\times10^9$/L) ($P=0.75$) and total length of hospitalization ($P=0.18$). Almost all patients (97.2%) had received broad-spectrum azoles (posaconazole or voriconazole) during induction. Only three patients, all in the fluconazole group, received fluconazole prophylaxis during the previous induction cycle. The time to onset of neutropenia from the first day of consolidation chemotherapy was similar between groups: fluconazole (median 10 days, range 3–12), posaconazole (median 10 days, range 6–34) and voriconazole (median 10 days, range 6–13). Similarly, the time to recovery from neutropenia was also comparable:

Table 4. Outcomes and probabilities as extracted from medical records

	Probability (%)		
Patient outcome	fluconazole ($n=30$)	posaconazole ($n=47$)	voriconazole ($n=29$)
Prophylactic success	93.33 ($n=28$)	80.85 ($n=38$)	93.10 ($n=27$)
Prophylactic failure	6.67 ($n=2$)	19.15 ($n=9$)	6.90 ($n=2$)
failure due to IFD	0.00 ($n=0$)	33.33 ($n=3$)	0.00 ($n=0$)
therapeutic success	0.00 ($n=0$)	66.67 ($n=2$)	0.00 ($n=0$)
death	0.00 ($n=0$)	33.33 ($n=1$)	0.00 ($n=0$)
failure due to intolerance	100.00 ($n=2$)	66.67 ($n=6$)	100.00 ($n=2$)

fluconazole (median 17 days, range 14–40), posaconazole (median 17 days, range 13–35) and voriconazole (median 17 days, range 13–40). The exceptions were two patients (one each in the fluconazole and posaconazole groups) with persistent pancytopenia at day 40.

The highest rate of prophylactic success occurred in the fluconazole group, followed by the voriconazole and posaconazole groups (Table 4). The weighted total duration of antifungal therapy (initial prophylaxis plus alternative therapies) was comparable among all groups: 32 days (median 35, range 15–43) with fluconazole, 30 days (median 32, range 10–61) with posaconazole and 32 days (median 31, range 17–67) with voriconazole.

Two patients encountered proven or probable breakthrough IFD (one case each) after receiving posaconazole prophylaxis for 12 and 16 days, respectively. One developed *Scedosporium prolificans* fungaemia and died 4 days later despite combination therapy with 500 mg of intravenous (iv) voriconazole on day 1 then 300 mg twice daily and 250 mg of oral terbinafine twice daily. Another had probable fungal pneumonia and was successfully treated with 26 days of iv liposomal amphotericin B at 3 mg/kg/day, sequentially combined with 20 days of 200 mg of oral voriconazole twice daily and then 10 days of 250 mg of terbinafine daily. The causative pathogen for this patient was not defined, despite fungal elements resembling *Aspergillus* spp. in the bronchoalveolar lavage specimen. The only case of suspected breakthrough IFD, also from the posaconazole group, received empirical antifungal therapy for pneumonia with iv liposomal amphotericin B at 3 mg/kg/day for 6 days, which was ceased after improvement. All these three patients had received posaconazole or liposomal amphotericin B prophylaxis during the previous induction cycle. The total duration of neutropenia following consolidation chemotherapy in the proven and probable cases (11 and 24 days, respectively) was not longer than that of patients with successful prophylaxis. No mucositis was recorded but both patients had symptomatic gastro-oesophageal reflux disease during consolidation chemotherapy. None had plasma posaconazole measured.

Overall, fluconazole, posaconazole and voriconazole prophylaxes were well tolerated. The frequency of premature discontinuation due to intolerance was highest in the posaconazole group (6/47, 13%) compared with the fluconazole (2/30, 7%) and voriconazole (2/29, 7%) groups (Table 4). If the initial prophylaxis was discontinued prematurely, alternative prophylactic therapies used included 100 mg of iv liposomal amphotericin B three times a week, 200 mg of oral posaconazole three times a day, 200 mg of oral fluconazole daily and 200 mg of oral voriconazole twice daily. Of the 10 patients who experienced intolerance, 50% had a history of intolerance to the oral formulation of that specific azole during previous induction chemotherapy; the majority of these (3/5) were in the posaconazole group. The rate of intolerance in the previous induction cycle was lower in the subgroup with prophylactic success (16.1%, 15/93).

Cost of antifungal prophylaxis

Fluconazole was the most cost-saving strategy (i.e. higher success and less costly than the alternatives), with savings of AU$8420 (26%) per patient over posaconazole and AU$3684 (13%) per patient over voriconazole (Table 5). Comparison between posaconazole and voriconazole resulted in a 14% disparity in overall cost (AU$32 799 versus AU$28 063 per patient, respectively). The averted treatment costs for IFDs constituted the major share of savings, in terms of hospitalization and antifungal drug therapies, of fluconazole over posaconazole. For the cost saving of fluconazole over voriconazole, its lower drug acquisition cost appeared to be the most important. Hospitalization was the primary driver of the total therapy cost (Figure 2).

Sensitivity analyses

In the scenario where patients in the three groups were matched (1:1:1) according to age (<60 and ≥60 years), 37 patients (fluconazole, $n=6$; posaconazole, $n=24$; voriconazole, $n=7$) were excluded. The economic advantage of fluconazole ($n=23$) over posaconazole ($n=23$) further increased to AU$11 227 per patient (30%), whereas the economic advantage of fluconazole over voriconazole ($n=23$) was slightly reduced (AU$2717 per patient or 10%) compared with the base case. The cost difference between posaconazole and voriconazole increased from AU$4736 (base case) to AU$8510 per patient (i.e. 23%) in favour of voriconazole.

Likewise, in the hypothetical situation of no IFD breakthrough in the posaconazole cohort ($n=44$), fluconazole remained dominant, with a 21% cost saving (AU$6401 per patient) over posaconazole. The economic difference between the two mould-active agents was reduced to 9% (AU$2717 per patient).

A ±50% variation in a single model parameter (i.e. the antifungal drugs' acquisition costs, hospitalization cost, total duration of hospitalization, daily dose of fluconazole, or exclusion of the costs of monitoring, diagnostic tests and outpatient clinic visits) had no substantial influence on the model's

Table 5. Proportional costs of prophylactic fluconazole, posaconazole and voriconazole

Patient outcome	Fluconazole			Posaconazole			Voriconazole		
	proportion (%)	cost (AU$)/ patient	proportional cost (AU$)	proportion (%)	cost (AU$)/ patient	proportional cost (AU$)	proportion (%)	cost (AU$)/ patient	proportional cost (AU$)
Prophylactic success	93.33	23681	22102	80.85	29693	24006	93.10	26 910	25054
Prophylactic failure									
failure due to IFD									
therapeutic success	—	—	—	4.26	78643	3347	—	—	—
death	—	—	—	2.13	29931	637	—	—	—
failure due to intolerance	6.67	34162	2278	12.77	37671	4809	6.90	43639	3009
Total cost per patient[a]			24380			32799			28063

[a]Individual costs may not add up to total costs because of rounding.

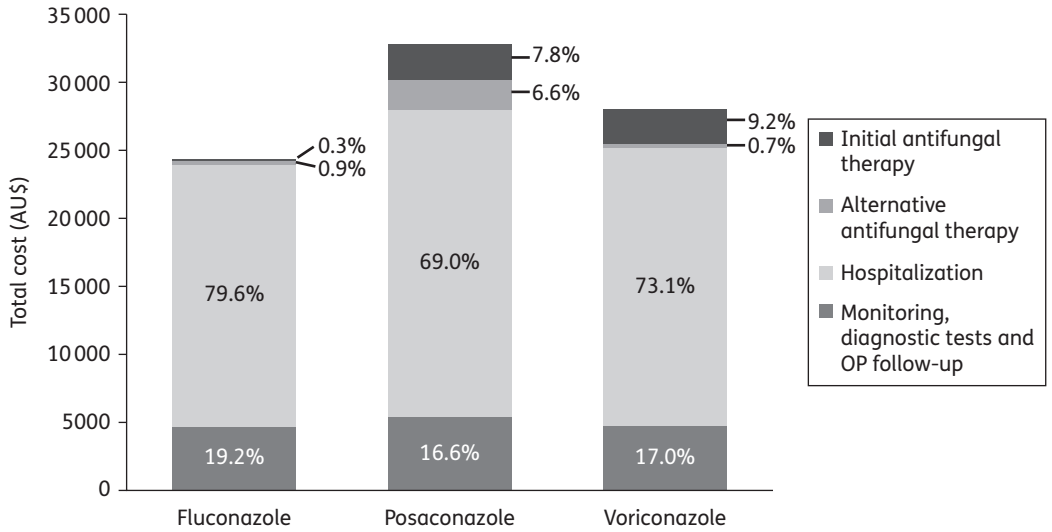

Figure 2. Contribution of different cost components to overall therapy. OP, outpatient.

conclusions. Threshold analyses indicated that posaconazole and voriconazole afforded cost saving over fluconazole only if the total duration of hospitalization was shortened from 19 to 12 days and from 17 to 14 days, respectively, or if the length of hospitalization associated with fluconazole increased from 17 to 24 or 20 days, respectively.

Probabilistic sensitivity analyses

Comparing posaconazole with fluconazole, Monte Carlo simulation showed a mean cost difference of AU$8430 per patient (95% CI AU$5803–AU$11 054) in favour of fluconazole. Fluconazole had >99.9% chance of conferring cost saving over posaconazole, ranging from AU$4102 to AU$12892 (Figure 3). The impact of clinical variables on the main conclusion is illustrated in Figure 4, which demonstrates that the cost difference was most sensitive to the treatment success in the fluconazole and posaconazole groups. This is unsurprising given that the proportions of patient distribution and associated costs were most substantial with these two variables (Table 5). Fluconazole also presented a mean cost saving of AU$3681 per patient (95% CI AU$990–AU$6319) over voriconazole with 99.8% probability (data not shown).

In comparing the two mould-active agents, voriconazole was preferred over posaconazole, attributed to its conferred saving at AU$4714 per patient (95% CI AU$1977–AU$7508) (data not shown).

Discussion

To our knowledge, this is the first study comparing the clinical and economic outcomes of fluconazole, posaconazole and

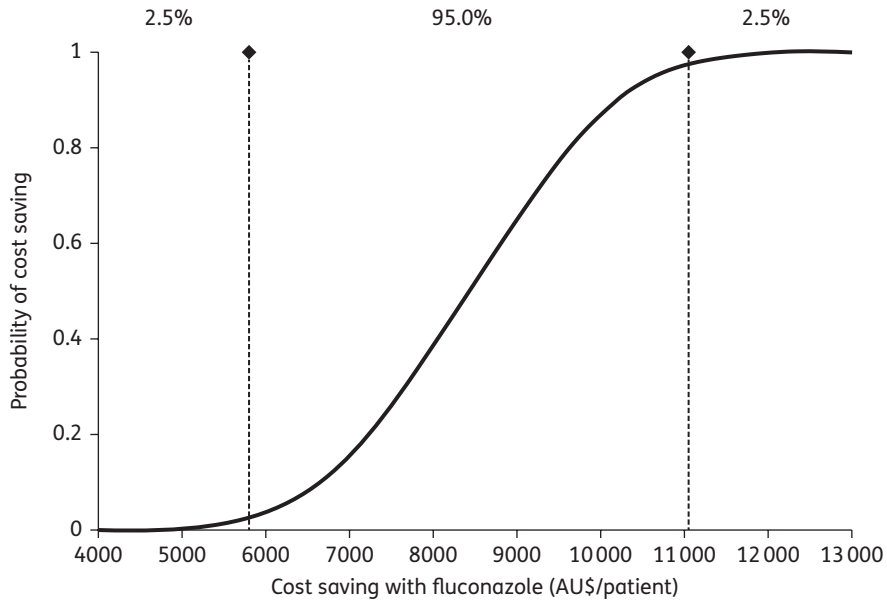

Figure 3. Cost saving probability curve of fluconazole versus posaconazole.

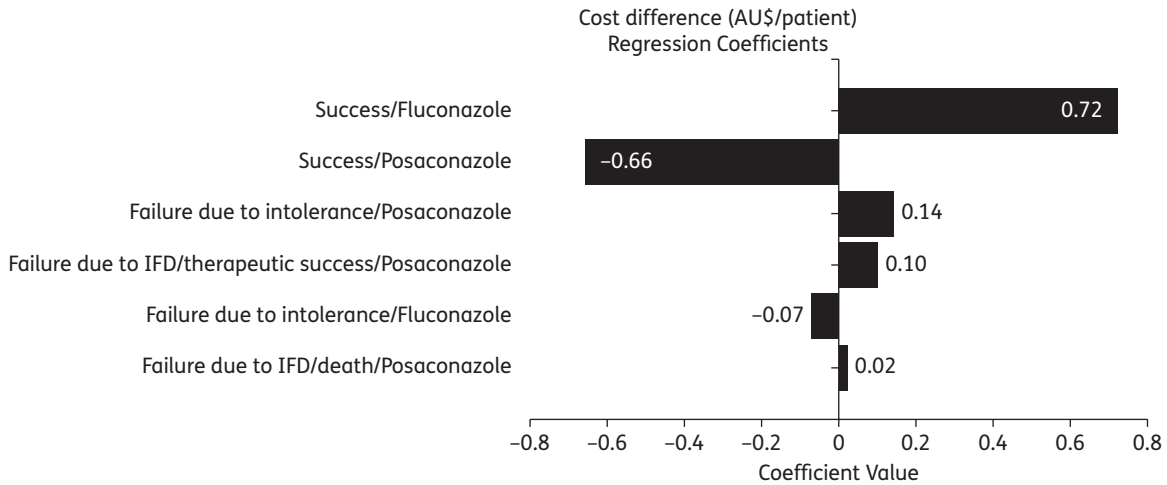

Figure 4. Tornado diagram of the regression of clinical variables on the cost difference between fluconazole and posaconazole. The study model was consistent with cost saving with fluconazole compared with posaconazole. Of the potential variables, prophylactic success in the fluconazole group exerted the greatest influence (regression coefficient 0.72) on the cost difference, increasing the cost saving associated with fluconazole. The second important variable was prophylactic success in the posaconazole group (regression coefficient −0.66), which reduced the economic advantage of fluconazole and minimized the cost difference.

voriconazole as antifungal prophylaxis during consolidation chemotherapy for AML. The strength of this study includes the utilization of actual clinical data to fully capture the downstream clinical and economic consequences after antifungal prophylaxis, depicting the real-world scenario. Furthermore, the costing period covered the total duration where patients are at risk of IFD after chemotherapy, including expenditure incurred throughout outpatient stay(s) and elective re-admission(s).

The main findings in this study are that the incidence of IFD was low in all groups and fluconazole prophylaxis (with a lower drug acquisition cost) was as effective and led to cost saving (26% and 13% reduction in overall costs over posaconazole and voriconazole, respectively). Determination of the incremental–cost effectiveness ratio was therefore not performed. Between the two mould-active agents, voriconazole conferred a 14% cost advantage over posaconazole. Therapeutic drug monitoring (TDM) and newer diagnostic tests (serum galactomannan antigenaemia test and *Aspergillus* PCR) were not part of standard practice during the study period and were used in only a small number of cases (<2%). Such costs were therefore excluded from our analysis, noting that inclusion of TDM costs would add to the cost advantage of fluconazole prophylaxis as TDM is recommended for posaconazole and voriconazole but not fluconazole.[12]

It is important to note that the baseline characteristics of the three patient groups were evenly matched with respect to risk factors for IFD. Specifically, there was no significant difference in the baseline characteristics across all groups, including duration of neutropenia and the use of intensive (cytarabine dose, $\geq$1.5 g/m^2/day) consolidation regimens. Significantly, almost all patients had received mould-active prophylaxis during their remission-induction chemotherapy.

The overall incidence of proven and probable IFD (2%) was similar to previous clinical observations (3.0%–4.5%).[25,26] Indeed, the risk of IFD in consolidation is lower than that in induction chemotherapy (8% with fluconazole prophylaxis).[11] This may reflect a number of factors, including the absence of colonization due to anti-mould prophylaxis in induction chemotherapy, patient selection such that only fit patients in remission receive consolidation, and a shorter duration of severe (absolute neutrophil count $<0.2\times10^9$/L) neutropenia. In comparison with induction chemotherapy, consolidation is less intense and most patients have a normal neutrophil count at the start of treatment. Less intensive chemotherapy may also result in less mucositis (i.e. lower risk of IFD) and better absorption of orally administered antifungal prophylaxis.

The current findings challenge the need for universal prophylaxis with broad-spectrum antifungals during consolidation chemotherapy in patients who have not developed an IFD during induction chemotherapy. At our observed incidence rate, the number needed to treat to prevent one IFD with posaconazole prophylaxis would be 52, not 16 as reported by Cornely *et al*.,[11] in a group that comprised predominantly patients receiving induction cycles. Our data suggest that in patients who received broad-spectrum antifungals during the high-risk remission-induction period, de-escalation to fluconazole is feasible in the consolidation cycles, together with a diagnostic-driven approach to detect early IFD.[36]

In this study, premature discontinuation due to intolerance occurred at a higher frequency in patients receiving posaconazole compared with those in the voriconazole and fluconazole groups. Posaconazole prophylaxis was usually discontinued because of diarrhoea, nausea, vomiting or poor oral intake, which could be either due to adverse effects of the drug or a consequence of consolidation chemotherapy. Concerns about reduced oral bioavailability and sub-optimal concentrations of posaconazole and voriconazole were the primary reasons for switching to iv liposomal amphotericin B therapy. The discontinuation rates of azole prophylaxis in this study contrast with the literature. The incidence of posaconazole discontinuation (13%) was lower than the 22% reported by Ananda-Rajah *et al*.[37] in AML induction, but higher than the 0% reported in the Cologne AML induction cohort.[19] The favourable tolerability profile of voriconazole (7% discontinuation) contrasted with the 15%[18] and 32.5%[38] discontinuation rates among AML patients, predominantly due to hepatotoxicity. No hepatotoxicity was observed in our cohort. The discontinuation rate with fluconazole prophylaxis (7%) in this study contrasted with the 22% rate previously reported.[38]

This study has limitations owing to the non-contemporaneous cohorts, primarily with the voriconazole group (2003–08) versus posaconazole (2006–10) and fluconazole (2005–09) groups. Posaconazole would therefore not have been a viable alternative for patients who discontinued the initial voriconazole prophylaxis due to side effects or other medical reasons, as posaconazole was not available in Australian public hospitals prior to 2006. Nevertheless, the small number of patients who discontinued voriconazole ($n=2$) in this study would have diminished the impact of this limitation on our study's conclusions. Even if voriconazole was discontinued due to intolerance, posaconazole, which is only available in oral formulation, would probably not have been considered a viable alternative. Another limitation flows from the clinicians' preference for the different antifungal drugs, which stems from the different levels of evidence in their efficacy as prophylactic agents. Given that posaconazole has the best evidence for its efficacy and survival benefit in the prophylaxis setting, clinicians may have had a lower threshold to discontinue voriconazole and fluconazole prophylaxis in cases of suspected IFD or deteriorating clinical condition. This would lead to switching to alternative antifungal treatment and increased overall costs. However, breakthrough IFDs only occurred in patients receiving posaconazole, thus reducing the importance of this limitation. Moreover, the presence of this confounder would result in higher alternative treatment costs for the fluconazole and voriconazole groups, and favour posaconazole prophylaxis, but we found that fluconazole has >99.9% chance of costing less than posaconazole, implying a minor influence of clinicians' discontinuation threshold on our findings. The 4.2% (2/47) incidence rate of proven or probable IFD observed with posaconazole prophylaxis was unusual, given that a lower breakthrough rate was found in clinical trials.[11,39] Excluding all IFD cases from the posaconazole group had no impact on the economic conclusion. Although the individual side effects associated with each of the three comparative drugs were not reported, the side effects were still considered in this study in terms of their indirect effects on the success and failure of therapies. The retrospective observational design and the size of the study cohort were also limitations, although it is, to our knowledge, the largest study of its kind to date.

In conclusion, the results of this study suggest that patients with AML who have successfully received broad-spectrum antifungal prophylaxis in induction cycles are predisposed to a low risk of acquiring IFD during their first cycle of consolidation chemotherapy. Fluconazole appears to be cost-effective in this group of patients, compared with posaconazole and voriconazole. In the context of readily available high-resolution CT scans, the galactomannan assay, *Aspergillus* PCR and other non-culture-based tests, it could be argued that fluconazole prophylaxis with a diagnostic-driven management strategy is adequate during consolidation chemotherapy for AML in patients without prior IFD.

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Transparency declarations

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