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The cost–utility analysis of antifungal prophylaxis for invasive fungal infections in acute myeloid leukaemia patients receiving chemotherapy: a study from a middle-income country

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SUMMARY

Background: Invasive fungal infections (IFIs) contribute to morbidity and mortality during acute myeloid leukaemia (AML) treatment. Without prophylaxis, IFI rate during AML treatment in Thailand is high and results in a high mortality rate and a prolonged hospital stay.

Aim: To evaluate the cost–utility of antifungal therapy (AFT) prophylaxis during AML treatment.

Methods: We assessed the cost–utility of AFT available in Thailand, including posaconazole (solution), itraconazole (solution and capsule), and voriconazole. A hybrid model consisting of a decision tree and the Markov model was established.

Results: The costs to prevent overall IFI using any AFT were all lower than the treatment cost of a non-prophylaxis group, resulting in a saving of 808–1507 USD per patient. Prevention with voriconazole prophylaxis showed the highest quality-adjusted life years (QALYs = 3.51, incremental QALYs = 0.23), followed by posaconazole (QALYs = 3.46, incremental QALY = 0.18) and itraconazole solution (QALYs = 3.45, incremental QALYs = 0.17). Itraconazole capsule reduced QALY in the model. For invasive aspergillosis prevention, posaconazole and voriconazole both resulted in better QALYs and life year

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savings compared with no prophylaxis. However, posaconazole prophylaxis was the only cost-saving option (976 USD per patient).

Conclusion: Posaconazole, itraconazole solution and voriconazole were all cost saving compared with no prophylaxis for overall IFI prophylaxis, with voriconazole being the most cost-effective option. Posaconazole and voriconazole were both cost effective for invasive aspergillosis prevention but only posaconazole was cost saving. A change in reimbursement policy for the use of AFT prophylaxis during intensive AML treatment could provide both clinical benefits to patients and substantial economic benefits to healthcare systems.

Introduction

Invasive fungal infection (IFI) is a severe complication that usually occurs during a remission-induction chemotherapy of acute myeloid leukaemia (AML). It is difficult to treat and significantly impacts both patient outcomes and economic burden for AML treatment [1]. Without prophylaxis, the incidence of probable/proven IFI is 10—20 % in AML patients receiving first induction chemotherapy, and it contributes to 20—30 % mortality [1—6]. IFI is also associated with prolonged hospital stays and poorer survival in this group of patients [7,8].

To make a diagnosis and treat IFI, multiple processes, including laboratory investigation, radiologic evaluation, and prolonged antifungal drug prescription, are required, leading to a high total direct medical cost of IFI treatment [9]. Several studies have shown the monetary and health benefits of antifungal drug therapy (AFT) prophylaxis in AML treatment, but most were conducted in high-income countries [10—14]. Even though IFI prophylaxis with AFT during AML treatment is recommended in most international treatment guidelines, preventing IFI by AFT is not routinely used in clinical practice in many resource-limited countries due to the high cost and the availability of AFT [4,5,15,16]. A previous publication from our group showed a high incidence of IFI among AML patients in a non-prophylaxis setting with a significant impact on increasing mortality and prolonged hospitalization [5]. This finding raised the question of whether the implementation of an IFI prophylaxis protocol in our setting might be cost effective despite the high price of prophylaxis medication.

Measures can be used to prevent IFI during AML treatment, such as treating patients in a controlled environment and prescribing antifungal prophylactic drugs. However, without AFT, other infection-control methods alone are inadequate for fungal prevention in most settings [17]. There are several antifungal agents that could be classified as AFT [18—24]. However, triazole drugs are the most popular AFT because they have low toxicity and are available in oral form.

New-generation azoles, such as posaconazole and voriconazole, are more effective against mould and may reduce mortality rate over the standard azoles therapy (SAT) [10,11,25,26]. Fluconazole, which is effective in preventing yeast infections but not mould infections, was recommended by the European Conference on Infections in Leukaemia (ECIL) in the setting of low mould incidence [27]. Our data from Thailand showed that moulds were the most common causative pathogens (93.1 %) of IFI during intensive treatment of AML [5]. Considering the high prevalence of moulds from our previous studies [5,28], we included only the mould-active triazoles, namely itraconazole, voriconazole and posaconazole in this cost—utility model analysis.

In Thailand, a one-month course of IFI prophylaxis, particularly with mould-active agents, is expensive compared with the cost of other medications. The concern over the cost of AFT would hinder the chance to make prophylactic AFT during AML treatment reimbursable, subsequently preventing the widespread use in routine clinical practice in Thailand. Economic evaluation to determine the monetary and health impact of IFI prophylaxis with AFT in this group of patients is essential for placing the medication into the national essential medication list (NEML) and thus to lead to routine clinical practice change in Thailand. Therefore, this study aims to evaluate the cost—utility of IFI prophylaxis using AFT during AML chemotherapy in Thailand, a middle-income country with a high prevalence of IFI.

Methods

Study population

All adults (age $\geq$18 years) newly diagnosed with AML coded according to the ICD-10 system as C92.0, C92.3, and C92.5—C92.9 between 1st January 2012 and 31st December 2015, were included when they met the following inclusion criteria: (1) admitted at Siriraj hospital for the initiation of chemotherapy with 3 + 7 regimen followed by three cycles of high-dose cytarabine (HiDAC) regimen, without receiving any antifungal prophylaxis; (2) medical records available from the date of diagnosis either to the date of death or the end of the first standard course of chemotherapy (100 days after diagnosis). We collected the actual treatment costs in patients who had received full standard courses of AML chemotherapy. The survival data of AML patients were retrieved from the total cohort of patients diagnosed at Siriraj between 2007 and 2016. This study was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (under COA no. Si 681/2015 and Si 212/2016).

Model structure

A hybrid model consisting of a decision tree and the Markov model, illustrated in Figure 1, was utilized to investigate the relevant costs and health outcomes. The model simulations began with the decision node, in which patients were randomly assigned to receive any of the four AFTs or no prophylaxis. AFT in our analysis included current anti-mould agents available in

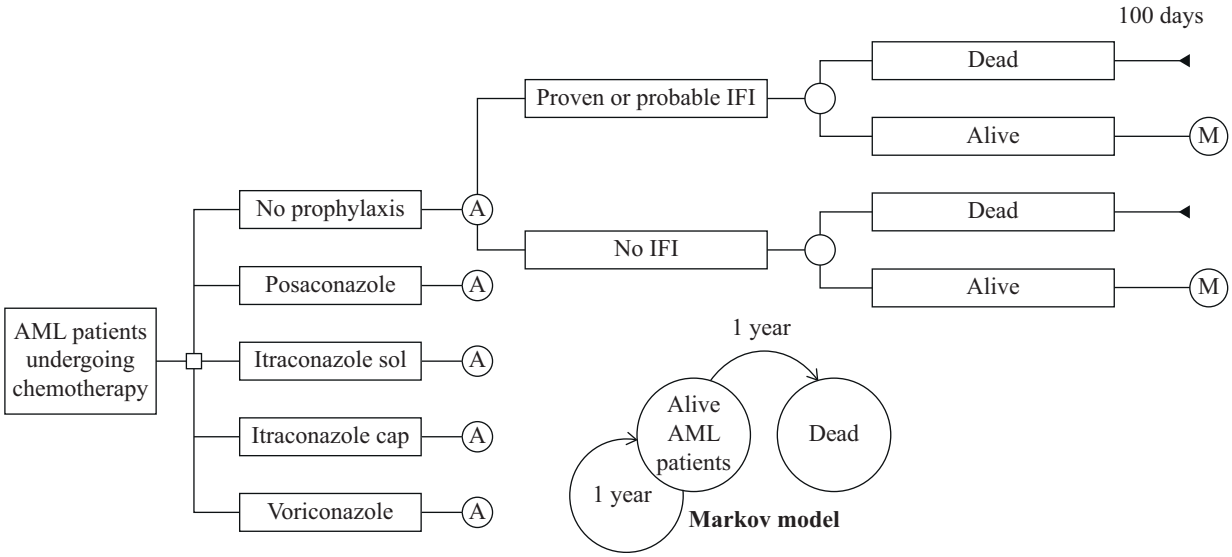

Figure 1. Schematic diagram of the combination of decision tree and Markov model used in this study. AML, acute myeloid leukaemia; cap, capsule; IFI, invasive fungal infection; M, Markov model; sol, solution.

Thailand, including itraconazole (solution and capsule), posaconazole (solution) and voriconazole. Each branch of the decision tree reflected the course of the disease over 100 days, the follow-up time after AFT that most of the research used [14,29—31]. The probability of IFI occurrence and death was simulated using inputs from relevant clinical variables. Those patients in the 'alive' groups were entered into the Markov model with a one-year cycle and simulated for a lifetime time horizon. We decided to use a one-year cycle in the Markov model as this was the estimated time to complete the course of treatment for patients with AML. Provided that the clinical outcome was significantly affected during the first year and reasonably steady afterwards in our cohort [32], we considered the cost in the first year separately then the following year with similar costs. Discounting at a rate of 3 % per year was used for the costs and health outcomes according to guidelines recommended in Thailand [33].

Clinical variables

Transition probabilities of the non-prophylaxis group in the model were based on the data from the AML 10-year-cohort at Siriraj Hospital [5], including the probability of IFI without antifungal prophylaxis, mortality in non-IFI patients and IFI-related mortality in IFI patients (Table I). For IFI cases, we decided to include both proven and probable IFI as they were deemed to require a similar approach in clinical practice. There were two scenarios: Scenario I — the overall IFI scenario, to see a prophylactic effect of AFT on the overall proven or probable IFI incidence; and Scenario II — the invasive aspergillus infection scenario, to see a prophylactic effect of AFT on the reduction of invasive aspergillosis incidence. We compared outcomes and costs with those of the non-prophylaxis group. The short-term clinical outcomes of treatments were categorized as alive or dead at 100 days after initiation of chemotherapy. The alive group was then explored and calculated for the annual probability of death in the Markov model. The clinical efficacy expressed in life-years (LYs) saved among patients in each AFT arm was investigated using results from a network meta-analysis study [14].

Cost variables

The study was taken from a societal perspective as recommended by Thailand's health technology assessment guidelines [34]. Both direct medical and non-medical costs were included in the analysis. In the non-IFI group, the actual medical costs occurred during admissions or outpatient AML and IFI treatment visits, including medical costs, nursing care costs and service fees (Table I). In the IFI group, the cost was collected from patients with invasive pulmonary aspergillosis or candidaemia, which included the same types of costs as the non-IFI group. The cost of prophylactic antifungal agents calculated for 21-day prophylaxis for the first induction chemotherapy cycle was added to direct medical costs using the price from the Thai national drug information database [35]. The direct non-medical costs (i.e., food and travel costs) per hospital visit were collected from the standard cost list [36]. All costs were adjusted to Thailand's consumer price index in 2023 [37]. We calculated the lifetime cost by using the Markov model. All costs were presented in Thai Baht (THB) and converted to US dollars (USD) (using an exchange rate of 1 THB = 0.031 USD, January 2023).

Quality of life variables

The utility was the outcome of interest for our study, which was evaluated using quality-adjusted life years (QALYs). Utility scores of AML patients were obtained from interviewing 34 AML patients who were alive after 100 days of the chemotherapy course. We used a Thai version of the European Quality of Life — 5 Dimensions — 3 Levels (EQ-5D-3L) questionnaire for the interview [38]. The survival of AML patients was retrieved from the cohort of patients diagnosed between 2007 and 2016. QALYs were then calculated from the LYs gained and the utility index derived from EQ-5D-3L.

Table I
Parameters for acute myeloid leukaemia (AML) patients undergoing chemotherapy used in the model

Parameters	Mean	SE	Distribution	Source
During 100 days after initiation of CMT				
Probability of IFI without antifungal prophylaxis	0.25	0.04	Beta	[5]
Probability of death in non-IFI patients	0.11	0.03	Gamma	[5]
Probability of death by IFI in IFI patients	0.32	0.04	Gamma	[5]
Prophylaxis effect of overall IFI incidence (odds ratio)				
Posaconazole	0.13	0.06	Gamma	[14]
Itraconazole solution	0.24	0.08	Gamma	[14]
Itraconazole capsule	0.51	0.35	Gamma	[14]
Voriconazole	0.17	0.09	Gamma	[14]
Prophylaxis effect of invasive aspergillus incidence (odds ratio)				
Posaconazole	0.12	0.15	Gamma	[14]
Itraconazole solution	1.11	0.55	Gamma	[14]
Itraconazole capsule	0.51	3.89	Log normal	[14]
Voriconazole	0.75	0.48	Gamma	[14]
Prophylaxis effect of IFI-related mortality in AML patients (odds ratio)				
Posaconazole	0.14	0.10	Gamma	[14]
Itraconazole solution	0.33	0.14	Gamma	[14]
Itraconazole capsule	1.36	2.69	Gamma	[14]
Voriconazole	0.12	1.01	Log normal	[14]
Direct non-medical costs (each visit), USD (THB)				
Cost of travelling	4.75 (153.34)	0.39 (12.48)	Gamma	[36]
Cost of food	2.07 (66.76)	0.21 (6.80)	Gamma	[36]
Number of OPD visits				
IFI alive patient	5.31	0.66	Gamma	Siriraj AML cohort
IFI death	1.8	0.43	Gamma	Siriraj AML cohort
Non-IFI alive	4.38	0.25	Gamma	Siriraj AML cohort
Non-IFI death	1.00	0.21	Gamma	Siriraj AML cohort
Direct medical costs — OPD, USD (THB)				
IFI alive patient	4146.46 (133,756.83)	726.62 (23,439.38)	Gamma	Siriraj AML cohort
IFI death	221.12 (7133.00)	135.40 (4367.83)	Gamma	Siriraj AML cohort
Non-IFI alive	749.71 (24,184.08)	154.55 (4985.56)	Gamma	Siriraj AML cohort
Non-IFI death	131.08 (4228.29)	54.77 (1766.75)	Gamma	Siriraj AML cohort
Direct medical costs — IPD, USD (THB)				
IFI alive patient	17,545.44 (565,981.92)	2252.14 (72,649.69)	Gamma	Siriraj AML cohort
IFI death	27,287.38 (880,238.00)	5892.38 (190,076.85)	Gamma	Siriraj AML cohort
Non-IFI alive	15,114.06 (487,550.20)	992.99 (32,032.07)	Gamma	Siriraj AML cohort
Non-IFI death	11,274.67 (363,699.00)	2220.45 (71,627.36)	Gamma	Siriraj AML cohort
Antifungal prophylaxis costs (per 21 days), USD (THB)				
Cost of posaconazole solution (600 mg OD)	1395 (45,000.00)	139.5 (4,500.00)	Gamma	[35]
Cost of itraconazole solution (400 mg OD)	384.68 (12,409.04)	38.47 (1,240.90)	Gamma	[35]
Cost of itraconazole capsule (400 mg OD)	61.19 (1974.00)	6.12 (197.40)	Gamma	[35]
Cost of voriconazole (400 mg OD)	549.08 (17,712.24)	54.91 (1771.22)	Gamma	[35]
Antifungal prophylaxis cost (per 21 days), USD (THB)				
Cost of antifungal drug monitoring for 21 days	139.5 (4,500.00)	13.95 (450.00)	Gamma	[36]
After 100 days after initiation of CMT				
Number of OPD visits in the first year	10.99	0.67	Gamma	Siriraj AML cohort
Number of OPD visits in the other years	4.46	0.79	Gamma	Siriraj AML cohort
Direct medical cost — OPD, USD (THB), per year				
In the first year	162.64 (5,246.45)	52.20 (1,683.78)	Gamma	Siriraj AML cohort
In the other years	22.63 (730.02)	7.02 (226.51)	Gamma	Siriraj AML cohort
Direct medical cost — IPD, USD (THB), per year				
In the first year	15,206.43 (490,529.99)	1,652.73 (53,313.95)	Gamma	Siriraj AML cohort
In the other years	1,814.50 (58,532.41)	587.27 (18,944.05)	Gamma	Siriraj AML cohort
Mortality rate of AML patients				
In the first year in IFI	0.26	0.04	Beta	[5]

(*continued on next page*)

Table I (*continued*)

Parameters	Mean	SE	Distribution	Source
In the first year in non-IFI	0.18	0.03	Beta	[5]
In the other years	0.15	0.01	Beta	Siriraj AML cohort
Utilities in AML patients				
	0.81	0.05	Beta	Interview

IFI, invasive fungal infection; IPD, inpatient department; OPD, outpatient department; SE, standard error; THB, Thai baht; USD, United States dollar.

Data analysis

We presented our results with incremental cost-effectiveness ratio (ICER), defined as the difference between the total cost of the IFI prophylaxis group from the patient lifetime and the total cost of the non-IFI prophylaxis group divided by the difference between the QALY of the IFI prophylaxis group and the non-IFI prophylaxis group. ICER was the main outcome used to consider whether the treatment was cost-effective compared with the willingness to pay threshold at 4960 USD (160,000 THB) (1.2 GDP per capita) recommended by the Ministry of Public Health, Thailand [39].

Table I demonstrates the mean, standard error (SE), and distribution of input parameters used in the model. A probabilistic sensitivity analysis was performed using Monte Carlo simulation. We generated a thousand simulations that were run to yield a range of possible values for the input parameter. The beta distribution variables were proportional parameters such as the incidence of IFI, the mortality of IFI and non-IFI patients at 100 days and one year, and the mortality and the utility of AML patients after one year from treatment. Either gamma or log normal distribution could be used for right skewed parameters such as the AFT prophylaxis effect and all costs of the treatments. Because our analysis retrieved data from a meta-analysis, for some variables, the provided data was not suitable to run probabilistic simulation with limited number and high uncertainty. In those variables, we used the normal distribution in order to illustrate the probabilistic sensitivity analysis. This might result in a probabilistic but not a deterministic value [40].

Additionally, probabilistic sensitivity analysis was calculated by using cost-effectiveness plane (CE plane). This could show the relationship between incremental cost and incremental QALY. For deterministic sensitivity analysis, one-way sensitivity analysis was carried out to assess the effect uncertainties on all parameters.

Results

Prediction of clinical outcomes, cost and utility

To establish the model for utility analysis, we simulated the total costs, LYs and QALYs of AML patients with or without IFI based on a hypothetical cohort of 1000 patients from the probabilistic model (Table II). With these values, we demonstrated the cost–utility analysis of AFT by modelling scenario I for the prevention against the overall proven or probable IFI and scenario II: the invasive aspergillus infection scenario, to prevent invasive aspergillosis. In scenario I, the costs of preventing overall IFI using any AFT agents were all lower than the treatment costs of a non-prophylaxis group, resulting in a saving of 808–1507 USD per patient. Furthermore, most AFTs, except for the itraconazole capsule, were also associated with higher LYs and QALYs. Posaconazole prophylaxis contributed to the highest LYs and incremental LYs (LYs = 4.27, incremental LYs = 0.23), followed by voriconazole and itraconazole solution (LYs = 4.26, incremental LYs = 0.22), in comparison with the non-prophylaxis group (LYs = 4.04). Prophylaxis with all AFTs, except for the itraconazole capsule, resulted in better QALYs in comparison to the non-prophylaxis group. Voriconazole prophylaxis showed the highest QALYs (QALYs = 3.51, incremental QALYs = 0.23), followed by posaconazole (QALYs = 3.46, incremental QALY = 0.18) and itraconazole solution (QALYs = 3.45, incremental QALYs = 0.17). Prophylaxis with itraconazole capsules decreased QALY when compared with the non-prophylaxis group. Considering the health benefits and ICERs, all AFTs, except itraconazole capsule, were dominant strategies over no prophylaxis with a better QALY at lower overall costs. Provided that the results demonstrated three cost-saving interventions, we created the cost-effectiveness efficiency frontier (Supplementary Figure S1) comparing among all cost-saving options compared with no prophylaxis. The graph demonstrates that posaconazole was ruled out according to the extended dominance concept and the voriconazole was the most cost-effective option with the highest efficacy and cost savings.

In scenario II, for invasive aspergillosis prevention, only the posaconazole prophylaxis group had a lower cost of treatment than the non-prophylaxis group (cost savings of 976 USD per patient). As a result, posaconazole was the only dominant intervention in this scenario because it provided a lower cost with better LYs and QALYs compared with no prophylaxis. Prophylaxis with itraconazole solution and voriconazole resulted in 1450 and 401 USD additional costs, respectively. Itraconazole solution AFT contributed to incremental QALYs of 0.14 with ICER/QALY of 10,449 USD, and voriconazole AFT contributed to incremental QALYs of 0.23 with ICER/QALY of 1748 USD.

Uncertainty analysis

Cost-effectiveness plane

Voriconazole and posaconazole had the lowest ICER/QALY in the overall IFI and invasive aspergillus scenarios, respectively. We then conducted the cost-effectiveness (CE) plane analysis for these two AFTs. Figure 2 shows the benefits of AFT compared with non-prophylaxis. The incremental costs of AFT (y-axis) compared with incremental QALYs (x-axis) of 1000 samples from the Monte Carlo simulation were plotted in the CE plane. In the overall IFI scenario (Figure 2a), most of the samples in posaconazole prophylaxis were in the lower right-hand quadrant, which meant that they were both cost-saving

Table II
Model predictions of costs, life years (LYs) gain, and quality-adjusted life years (QALYs) of prescribing antifungal therapy (AFT) following standard chemotherapy in acute myeloid leukaemia (AML) patients in overall invasive fungal infection (IFI) scenario and invasive aspergillus infection scenario

Types of prophylaxis	Non-prophylaxis	Posaconazole	Itraconazole solution	Itraconazole capsule	Voriconazole
Overall IFI scenario					
Total cost per patient, USD (THB) [95% CI]	32,582.19 (1,051,038.33) [32,397.96–32,766.41]	31,665.18 (1,021,457.43) [31,477.01–31,853.35]	31,021.07 (1,000,679.61) [30,831.68–31,210.46]	31,126.03 (1,004,065.43) [30,872.88–31,379.18]	30,871.50 (995,854.98) [30,683.69–31,059.32]
LYs [95% CI]	4.04 [4.01–4.06]	4.27 [4.24–4.29]	4.26 [4.23–4.28]	4.11 [4.07–4.15]	4.26 [4.23–4.28]
QALYs [95% CI]	3.28 [3.25–3.30]	3.46 [3.44–3.49]	3.45 [3.43–3.48]	2.94 [2.81–3.07]	3.51 [3.49–3.53]
Incremental cost, USD (THB) [95% CI]		-917.01 (-29,580.90) [-965.85 to -868.17]	-1561.12 (-50,358.72) [-1606.36 to -1515.88]	-1456.16 (-46,972.90) [-1639.26 to -1273.06]	-1710.68 (-55,183.35) [-1760.42 to -1660.95]
Incremental LYs [95% CI]		0.23 [0.23–0.24]	0.22 [0.22–0.23]	0.07 [0.04–0,10]	0.22 [0.21–0.22]
Incremental QALYs [95% CI]		0.19 [0.18–0.19]	0.18 [0.17–0.18]	-0.34 [-0.46 to -0.21]	0.23 [0.20–0.27]
ICERs, USD (THB) [95% CI]		Dominant	Dominant	4335.87 (139,866.87) [-559.77 to 9231.52]	Dominant
Invasive aspergillus infection scenario.					
Total cost per patient, USD (THB) [95% CI]	32,799.75 (1,058,056.33) [32,611.27–32,988.22]	31,824.10 (1,026,583.90) [31,630.63–32,017.57]	34,445.80 (1,111,154.77) [34,210.03–34,681.57]	34,253.19 (1,104,941.60) [33,452.04–35,054.34]	33,255.47 (1,072,757.17) [33,027.66–33,483.28]
LYs [95% CI]	4.04 [4.02–4.06]	4.27 [4.24–4.29]	4.21 [4.19–4.24]	3.62 [3.46–4.78]	4.21 [4.18–4.24]
QALYs [95% CI]	3.28 [3.26–3.30]	3.47 [3.44–3.49]	3.42 [3.39–3.44]	2.94 [2.81–3.07]	3.51 [3.49–3.53]
Incremental cost, USD (THB) [95% CI]		-975.65 (-31,472.43) [-1032.53 to -918.76]	1646.05 (53,098.44) [1516.81 to 1775.29]	1453.44 (46,885.27) [675.43–2231.46]	455.73 (14,700.84) [335.81–575.64]
Incremental LYs [95% CI]		0.23 [0.22–0.23]	0.17 [0.17–0.18]	-0.42 [-0.58 to -0.26]	0.17 [0.16–0.18]
Incremental QALYs [95% CI]		0.19 [0.18–0.19]	0.14 [0.13–0.14]	-0.34 [-0.47 to -0.21]	0.23 [0.19–0.26]
ICERs, USD (THB) [95% CI]		Dominant	11,862.25 (382,653.17) [-30,172.03 to 53,896.53]	Dominated	1984.30 (64,009.62) [-8062.00 to 12,030.58]

CI, confidence interval; ICER, incremental cost-effectiveness ratio; THB, Thai baht; USD, United States dollar.

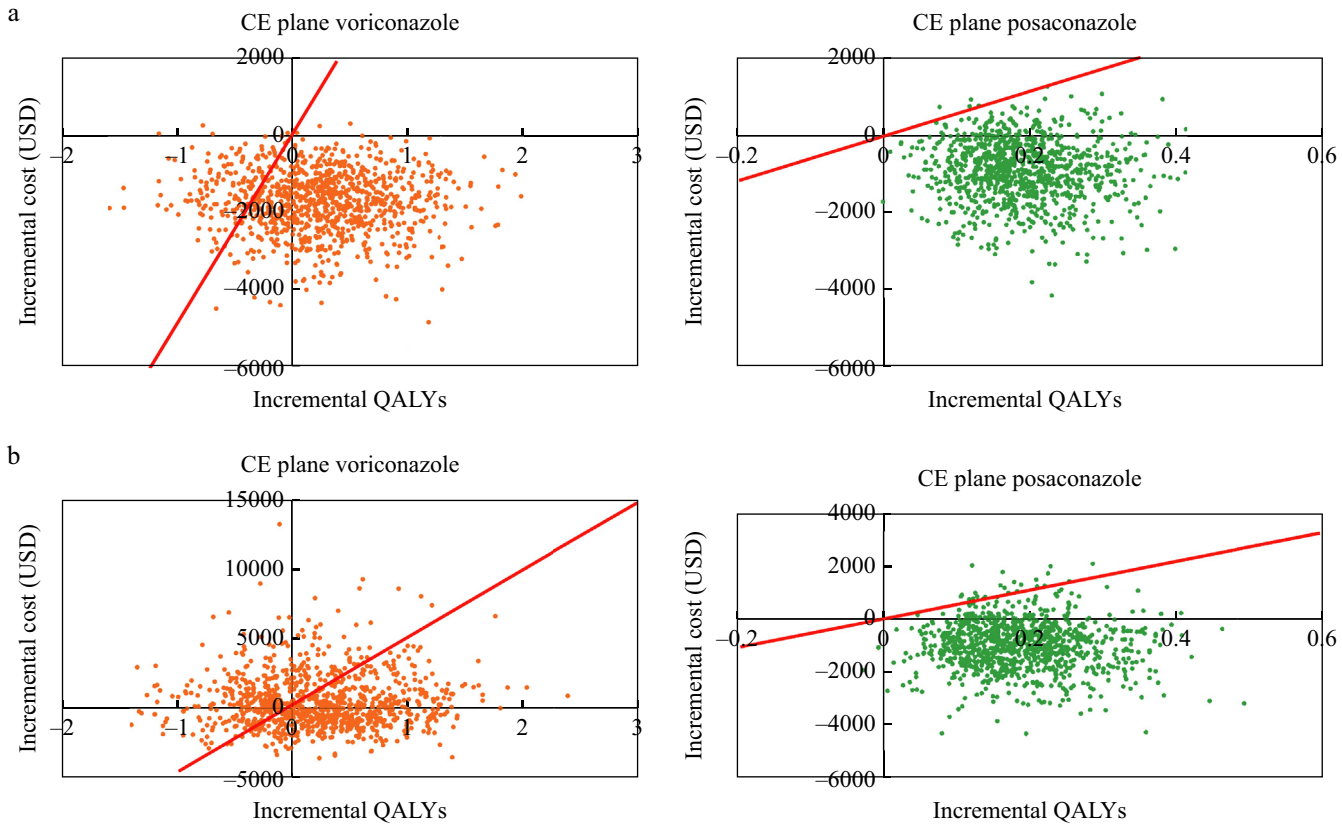

Figure 2. Cost-effectiveness plane of voriconazole and posaconazole prophylaxis in overall IFI scenario (a) and in invasive aspergillus infection scenario (b). The red line shows the willingness to pay threshold (4960 US dollars, 160,000 Thai bhat).

and showed quality-of-life improvements. However, almost all of the voriconazole samples were in the lower horizontal area, and only 67 % gained in QALYs. For the invasive aspergillus infection scenario (Figure 2b), posaconazole's result was still cost-saving and quality of life improvement, while only half of the voriconazole was cost-saving, only 65 % of them had gained in QALYs.

One-way sensitivity analysis

We conducted a one-way sensitivity analysis to investigate the influential factors on our cost–utility model by considering the lowest ICER in each scenario. The one-way sensitivity analysis demonstrated the change in ICER of voriconazole prophylaxis in overall IFI scenario (Figure 3a) and posaconazole prophylaxis in invasive aspergillus infection scenario (Figure 3b) with the top 10 associated parameters. The cost of in-patient department (IPD) treatment of IFI patients was the most influential factor for the cost effectiveness in both scenarios, followed by the efficacy of voriconazole and posaconazole prophylaxis. In comparison, the probability of IFI without antifungal prophylaxis should be considered in posaconazole prophylaxis in the invasive aspergillosis scenario.

Discussion

Supportive care during intensive treatment of AML is crucial to the treatment outcome of the patient. The use of antifungal prophylaxis in AML patients receiving chemotherapy has shown clinical benefits and life-saving potential in many clinical trials [14,29,30] and has, therefore, been recommended in several international guidelines [27,41]. However, the implementation of this strategy at national level with preferably reimbursement from the government would require cost effectiveness in the context of each country. Several studies showed the economic benefits of AFT prophylaxis in AML patients, but most of them were conducted in high-income countries. The data in the context of lower or middle-income countries were scarce, and most studies usually used a simplified cost-estimation model, which may not represent the actual outcome and cost in real-life situations [13,42,43]. The world bank has categorized Thailand as a middle-income country since 2011, with a current GDP of 505.95 billion USD and a GDP per capita of 7066.2 USD (as of 2021). Thailand has implemented universal health coverage (UC) for its population in 2002. However, high-cost medications would require economic evaluation data for each clinical indication in order to be reimbursed under the UC health scheme. Prophylactic therapy with AFT in patients with AML during chemotherapy is one of them. Without any IFI prevention, this clearly had a detrimental effect on the outcome of AML patients in our country [5]. Of note, no previous study compared the cost effectiveness of AFT with the newer-generation azoles with non-prophylaxis.

In the present study, we aimed to investigate the economic benefits of prophylactic AFT during AML treatments integrated with evidence of clinical efficacy, in Thailand's context using a decision-analytic model. As opposed to other studies that used an estimation of the additional cost of treating IFI [10,13,44],

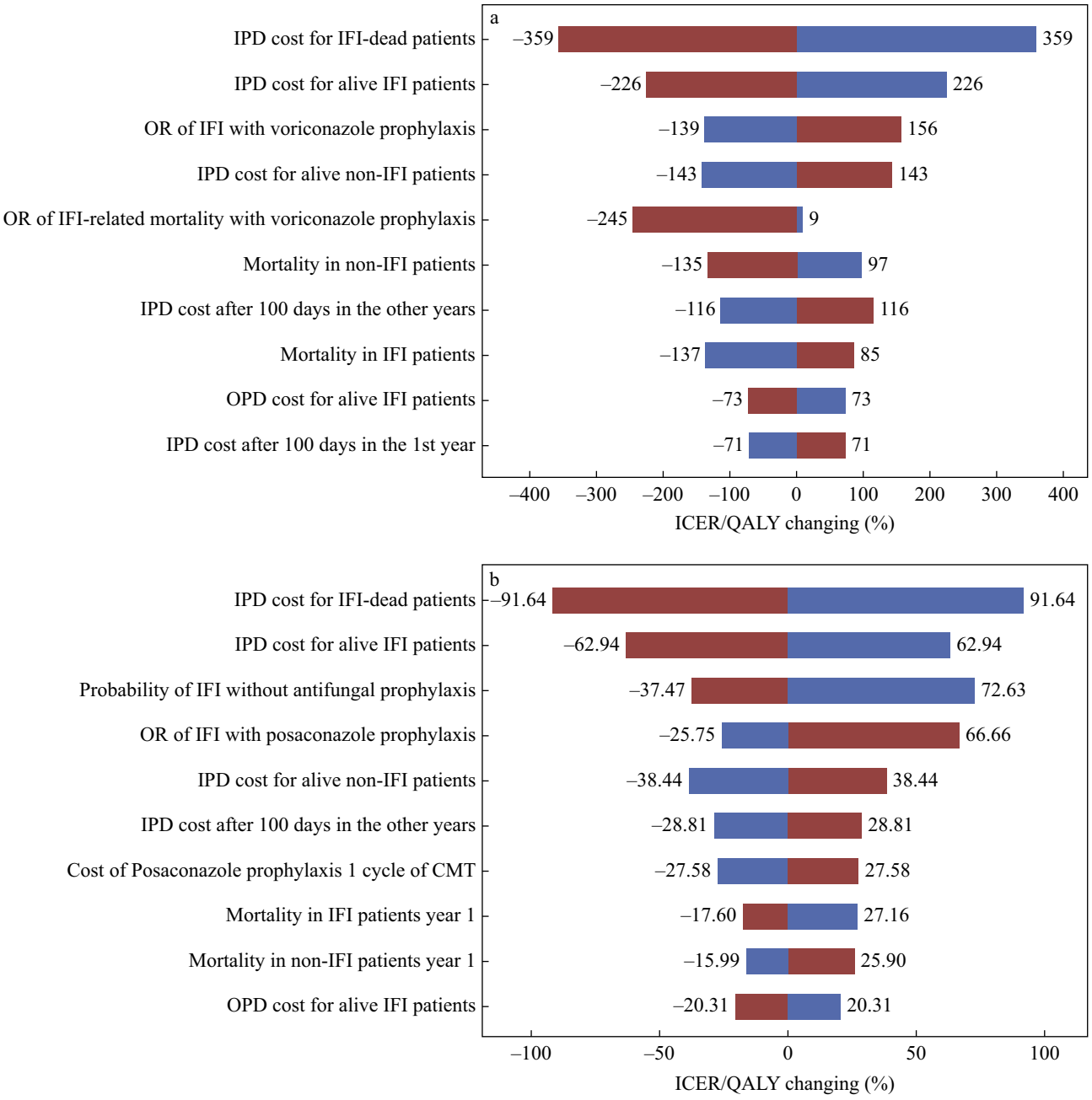

Figure 3. Tornado diagram for the incremental cost-effectiveness ratios (ICER) per quality-adjusted life-year (QALY) changing voriconazole prophylaxis in the overall IFI scenario (a) and posaconazole prophylaxis in the invasive aspergillus infection scenario (b). The solid vertical line represents the total ICER/QALY for the patient receiving chemotherapy and posaconazole or voriconazole prophylaxis, using the probability of overall invasive fungal infection (IFI) reduction. The horizontal bars represent the range of this difference when the corresponding single input is varied across its designated range with all other input parameters held constant. One-way sensitivity analysis of the cost of treatment for voriconazole prophylaxis. red: high range, blue: low range. CMT, chemotherapy; IPD, inpatient department; OPD, outpatient department; OR, odds ratio.

we collected comprehensive data on medical and non-medical expenses in treating AML patients with or without IFI complications. Moreover, we built a model based on our actual prevalence of IFI and clinical outcomes to reflect the real-life clinical and economic burden of IFI in our AML patients.

In our model, we found that all azoles, except the itraconazole capsule, prescribed as prophylaxis for overall IFI in AML patients during intensive chemotherapy treatment, were cost-saving options compared with a non-prophylaxis approach. According to the extended dominance concept explored in the CE frontier, voriconazole was considered the most cost-effective option with the highest efficacy along with the highest cost savings. In scenario II, both posaconazole and voriconazole were cost-effective agents in preventing invasive aspergillosis. Both of them resulted in better QALYs when compared with non-prophylaxis and their ICERs fell below the

willingness to pay threshold of Thailand. However, posaconazole was the only cost-saving option in this comparison.

Because all AFT prophylactic treatments except itraconazole capsules were effective and cost saving during AML treatment, in the setting where the incidence of mould infection was low, any AFT could be used as a prophylactic intervention. But the voriconazole could be considered as the most cost-effective option according to the extended dominance concept. However, in the setting where the incidence of mould infection, especially invasive aspergillosis, is high, posaconazole might be recommended over voriconazole considering both clinical efficacy and economic benefit according to our analysis.

Even though posaconazole and voriconazole have similar prophylactic effects for the overall IFI incidence (odds ratio (OR) 0.12 and 0.17, respectively) and IFI-related mortality (OR 0.14 and 0.12, respectively), the prophylaxis effect of posaconazole for invasive aspergillus infection was significantly higher than that of voriconazole (OR 0.12 and 0.75, respectively) [14]. Posaconazole has earned a recommendation from the ECIL to be used as first-line IFI prophylaxis [27] during AML intensive therapy due to the superior prevention and a clear survival benefit over conventional azoles in a randomized control trial [29]. Here, we showed an additional economic benefit of posaconazole in providing the highest LY gained with a significant reduction in treatment costs in the context of a middle-income country. Voriconazole, an alternative choice for prophylaxis recommended in the ECIL guidelines [27], also demonstrated cost-effectiveness benefits in our analysis. Our results affirm the monetary benefit of using posaconazole prophylaxis in AML patients undergoing chemotherapy in a setting with a high incidence of mould infection.

Our result was in accordance with previous studies that compared the benefit of posaconazole or voriconazole over SAT or amphotericin B in the context of both high-income countries [11,45,46] and middle-income countries [13,42,43,47]. Of note, previous cost-effectiveness studies of AFT were usually conducted in the context of allogeneic stem cell transplantation rather than during the chemotherapy phase of AML treatment. Interestingly, although posaconazole was the most expensive AFT, we determined from a societal perspective that it appeared to be the most attractive option for AFT prophylaxis, considering that it is the cost-saving AFT for both scenarios analyzed and the only option for aspergillosis prevention. The impressive economic benefits identified in our study could stem from the very high incidence of IFI and invasive aspergillus infection during AML treatment in Thailand [5] and the high cost of treatment and investigation for suspected and established IFI. However, voriconazole would be the best option in the scenario aimed at preventing overall IFIs, with the highest QALYs gained at the lowest total cost.

We conducted a one-way sensitivity analysis to determine the factors that impacted our cost—utility model. As shown in the tornado diagrams, the most influential factor in the ICER of voriconazole and posaconazole in our model was the in-patient costs for treating patients with IFI. Therefore, in a situation where the treatment cost of IFI is high, AFT prophylaxis would be more cost effective.

The cost of antifungal prophylaxis could vary in different countries. We observed that a report from Tang *et al*. from China showed that the cost of posaconazole prophylaxis was 2383.64 USD, which was higher than that of voriconazole (1925.62 USD) [24], whereas a study from Australia showed a comparable prophylaxis cost of posaconazole and voriconazole (666.4 vs 924.0 USD) [48]. In Thailand, the price of posaconazole per course is the highest among the four AFTs (posaconazole 1395.00 USD, itraconazole solution 384.68 USD, itraconazole capsule 61.19 USD, voriconazole 549.08 USD). Considering that the price of antifungal agents was identified to be one influential factor on ICER in the sensitivity analysis, the different prices in other settings might affect the results shown and the conclusions made compared with this study.

The strength of this study is creating an economic evaluation model that reflects a real-life situation by using actual clinical evidence and the cost of treatment. As a sponsorship in cost-effectiveness studies could produce a significant bias [49], the independent nature of this study allowed us to compare AFTs whilst minimizing conflict of interest. However, there are some limitations to the study. Firstly, because the use of AFT prophylaxis was not a routine clinical practice, the efficacy of each AFT was derived from a network meta-analysis study [14]. The cost of AFT prophylaxis was then calculated an integrated into the model. From this network meta-analysis, only two studies were conducted in Asian populations. The model did not consider the differences in drug pharmacokinetics among patient ethnicities, which might interfere with the plasma drug levels and the efficacy of AFT. Apart from that, isolation room and air treatment systems were scarce in our country. Therefore, we were aware that actual efficacies of AFT in the Thai population may vary from clinical trials performed in patients with different ethnicities and hospital infrastructures. Secondly, even though therapeutic drug monitoring (TDM) was recommended in order to improve efficacy and safety of AFT [27,50—52], we decided not to incorporate costs of TDM in our model because the studies included in our reference network meta-analysis did not use TDM guided dose adjustment and TDM is not yet available in Thailand nationwide. TDM could be an additional cost of AFT and may improve the efficacy of AFT prophylaxis. Further studies should be carried out to determine the cost effectiveness of TDM in IFI prophylaxis. In a situation where drug—drug interactions is a concern, posaconazole might be a better option [53].

Although prophylactic treatment with azoles has been considered expensive in the context of a middle-income country, our cost—utility analysis showed that AFT provided an economic and clinical benefit to AML patients undergoing chemotherapy. Interestingly, some AFTs not only improved QALY but were also cost-saving. Posaconazole had the highest monetary benefit for preventing overall IFI and aspergillus infection, while voriconazole had the highest probability for QALY gained and remained cost-effective for both scenarios. Our models implied that in a setting with high prevalence of mould infection, posaconazole should be the prophylactic agent of choice. The high prevalence of IFI in AML was evident in Thailand. Our results should encourage policy makers to implement changes in order to improve the quality of care for AML patients. We also encourage other researchers in lower-to middle-income countries to explore the economic analysis of AFT prophylaxis in their contexts.

Author contributions

T.P., D.D. and W.P. collected and analysed data, and drafted the manuscript; N.T. and S.M. analysed and drafted the manuscript; V.N., K.A., S.T., S.K., S.T. and W.J. collected data; M.C. supervised and gave critical interpretation of the study; V.S. and P.P. conceptualized, analysed, supervised, and gave the critical interpretation of the study; all authors contributed to the article, discussed, edited and reviewed the manuscript; all authors approved the submitted version.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary data

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