

Comparative cost-effectiveness analysis of voriconazole and fluconazole for prevention of invasive fungal infection in patients receiving allogeneic hematopoietic cell transplants

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Patients undergoing allogeneic hematopoietic cell transplantation (HCT) are at high risk for invasive fungal infections (IFIs), especially those caused by *Candida* species and *Aspergillus* species.¹ Given the high mortality rates associated with these infections and the high costs of their treatment, preventive strategies are now part of standard care.² Placebo-controlled trials in patients undergoing autologous or allogeneic HCT have shown that fluconazole decreases *Candida* infection and IFI-related deaths after HCT.¹ Only one study, which primarily enrolled allogeneic HCT recipients, showed a reduction in overall mortality associated with fluconazole prophylaxis.^{3,4}

Because fluconazole has no activity against *Aspergillus* species or other molds, randomized con-

Purpose. The cost-effectiveness of voriconazole versus fluconazole prophylaxis against fungal infections in hematopoietic cell transplant (HCT) recipients is investigated.

Methods. A decision-analytic model was developed to estimate the drug costs associated with planned or supplemental prophylaxis and empirical therapy and the costs of treating suspected or documented invasive fungal infections (IFIs) in HCT recipients. Published clinical trial data on 599 patients who received 100–180 days of prophylactic therapy with voriconazole or fluconazole were used to model specified IFI-prevention and mortality outcomes; 6-month, 12-month, and lifetime incremental cost-effectiveness ratios (ICERs) were estimated, with a bootstrap analysis performed to reflect the uncertainty of the clinical trial data.

Results. Estimated mean total prophylaxis and IFI-related costs associated with voriconazole versus fluconazole prophylaxis

over 12 months were higher in the entire study population and among patients receiving HCT for diagnoses other than acute myeloid leukemia (AML) but were not significantly different for patients with AML. The cost per IFI avoided (\$66,919) and the cost per life-year gained (\$5,453) were lower among patients with AML who received voriconazole relative to the full study population. ICERs were more favorable for voriconazole over a 6-month time frame and when modeling was conducted using generic price data. Assuming a threshold value of \$50,000 for one year of life gained, the calculated probability of voriconazole being cost-effective was 33% for the full study population and 85% for the AML subgroup.

Conclusion. The decision model indicated that voriconazole prophylaxis was cost-effective for patients undergoing allogeneic HCT for AML.

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trolled trials of prophylaxis with itraconazole, posaconazole, and voriconazole, drugs that are active against *Aspergillus* species, have been completed in patients undergoing allogeneic HCT.¹ In particular, Blood and Marrow Transplant Clinical Trials Network (BMT CTN) trial 0101 was a randomized, double-blind, multicenter study of fluconazole versus voriconazole for the prevention of IFI in allogeneic HCT recipients.⁵ Regular serum galactomannan monitoring for IFI was performed, and all participants were followed for up to 12 months, including at least 6 months after the end of planned prophylaxis (administered for either 100 or 180 days). The results of the trial indicated that voriconazole was not superior to fluconazole when considering the primary endpoint of fungal-free survival (i.e., patient alive and free from presumptive, probable, or proven IFI) at 6 months; prophylaxis with either voriconazole or fluconazole gave similar results. However, there were trends of fewer *Aspergillus* infections and less-frequent use of empirical antifungal therapy in patients receiving prophylaxis with voriconazole compared with those receiving prophylaxis with fluconazole.

The economic evaluation reported here used data from the BMT CTN 0101 clinical trial⁵ to estimate the cost-effectiveness of prophylaxis

with voriconazole compared with fluconazole in patients undergoing allogeneic HCT. Previous analyses have been performed to determine whether clinical benefits that have been shown using prophylaxis regimens that are active against both *Aspergillus* and *Candida* species might result in offsetting cost savings and favorable cost-effectiveness ratios.^{6,7} The clinical benefits that have been shown include a reduced need for empirical therapy and reduced cases of IFI.^{5,8-10} For the analysis described in this article, data were collected on IFI cases, all other prophylaxis regimens used during the clinical trial period, and empirical therapy for patients suspected of having an IFI, allowing for a more comprehensive assessment of the outcomes.

Methods

The study used a decision-analytic approach to estimate the costs and cost-effectiveness of voriconazole compared with fluconazole for prevention of IFI in patients receiving allogeneic HCT. Estimates were generated for all trial participants, including two subgroups within the trial population: patients with acute myeloid leukemia (AML) and those with other underlying diseases (i.e., acute lymphoblastic leukemia, chronic myelogenous leukemia, myelodysplastic syndrome, and non-Hodgkin's lymphoma). The

subgroup analyses were performed for two reasons. First, there was an imbalance in the numbers of AML patients in the two prophylaxis groups in the full study population; and second, there were greater risks of IFI and death and, in a post hoc analysis, a higher rate of fungal-free survival in the voriconazole cohort among patients with AML. As in the full study population, the numbers of patients with AML in the fluconazole and voriconazole cohorts were evenly balanced with respect to graft source (bone marrow versus peripheral blood), transplant type, and rate of graft-versus-host disease. In addition, the patients with AML in the two prophylaxis cohorts received immunosuppressant therapy similar to that of all trial participants. A bootstrap analysis was performed to represent the uncertainty in the BMT CTN trial results. Analyses of the sensitivity of the results to changes in oral voriconazole costs and IFI treatment costs were also performed.

Model structure. A decision-analytic approach was taken for the analysis (Figure 1). Three time periods were considered in the analysis: 6 months, 12 months, and lifetime. During the trial time period, a patient could be assigned to planned prophylaxis with either voriconazole or fluconazole. Within the 6- or 12-month time period, each patient could be either diagnosed or not

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diagnosed with a possible, presumptive, probable, or proven IFI and could either die or not die. Causes of death were classified as related to IFI or related to the underlying disease. The no-IFI branch of the decision tree included patients with no IFI and those with a possible IFI (i.e., the case met the clinical criterion for IFI [symptoms of a lower-respiratory-tract infection] but mycological confirmation was lacking), some of whom were given a short course of empirical therapy but never developed a presumptive, probable, or proven IFI as defined in the BMT CTN trial.⁵ The IFI branch of the decision tree included patients with one or more presumptive, probable, or proven IFIs. Because there were no statistical differences in the observed rates of adverse events associated with different types of prophylaxis in the clinical trial, adverse events were considered to occur equally in all branches of the decision tree, and the associated costs were not calculated separately. Table 1 presents a listing of the clinical outcomes of the BMT CTN study that were used to derive

the probabilities for the decision-tree model and for the measurement of cost inputs for the model.

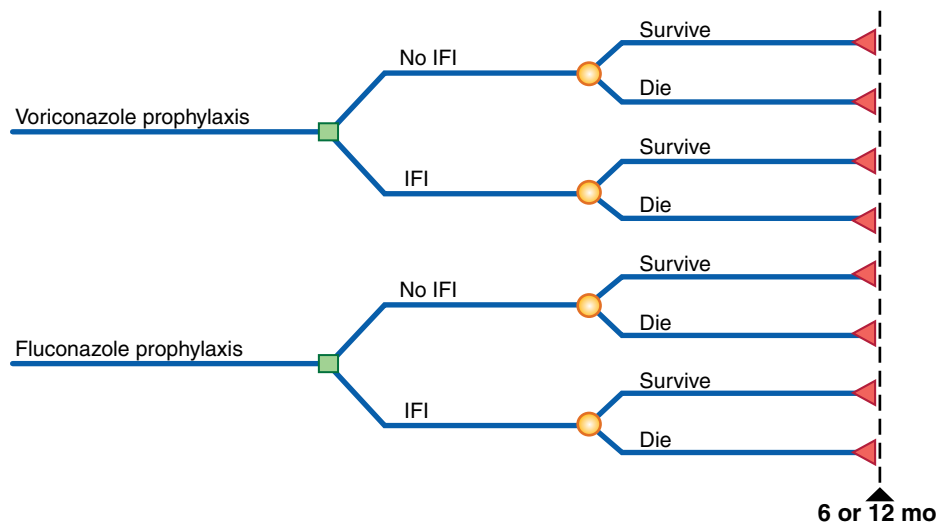
Study population. The study population included patients two years of age or older who (1) were receiving a related or unrelated hematopoietic graft for AML in first or second complete remission or early relapse; acute lymphoblastic, biphenotypic, or undifferentiated leukemia in first or second complete remission; chronic myelogenous leukemia in the chronic or accelerated phase; or myelodysplastic syndrome, or (2) were receiving a related donor transplant for chemosensitive non-Hodgkin's or Hodgkin's lymphoma.

Efficacy variables. The measure of effectiveness used in the 6- and 12-month cost-effectiveness analyses was the rate of presumptive, probable, or proven IFIs during those respective time periods. The IFI rates at 6 and 12 months were determined using competing risk models in which death was a competing risk. Deaths or infections that happened beyond the 12-month threshold (i.e., after 12 months or more had elapsed

from the day treatment started) were not considered. The time to first infection was considered for three patients with two IFIs each.

For the lifetime cost-effectiveness analysis, the primary benefit outcome of interest was average expected life-years. Life-years were estimated for each patient in the BMT CTN trial (both survivors and nonsurvivors of the antifungal prophylaxis period). Life-years for the nonsurvivors were estimated using the time to death during the trial. Life expectancy for each 1-year survivor was estimated as the product of (1) the remaining life expectancy (as determined using annual mortality rates for the general population from the 2004 United States life tables¹¹) according to sex, nationality, ethnicity, and age at the time of entry into the clinical trial, and (2) the annual relative risk of post-HCT mortality based on underlying disease, as estimated by Wingard et al.¹² in their study of data reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) on more than 10,600 HCT recipients worldwide.

Figure 1. Structure of decision tree used to model 6- and 12-month clinical outcomes (i.e., occurrence of invasive fungal infection [IFI], mortality) in hematopoietic cell transplant recipients receiving fluconazole or voriconazole prophylaxis.



The relative-risk data reported by Wingard and colleagues¹² did not include the relative risk of mortality compared with general population mortality rates from 1 to 2 years and more than 15 years after HCT; therefore, for the analysis described in this article, it was assumed that the relative risk of mortality from 1 to 2 years after HCT was equal to the relative risk from 2 to 3 years after HCT for each underlying disease; the relative risk after year 15 was assumed to remain constant and was calculated by averaging the relative risk of mortality for years 10–15 for each underlying disease, with life-years discounted at a rate of 3% annually.

The report of Wingard and colleagues¹² on the CIBMTR study also did not present data on HCT recipients with chronic myelogenous leukemia; thus, for the purposes of the analysis described here, the relative risk of mortality for patients in the CIBMTR study population with severe aplastic anemia disease (as reported by Wingard et al.) was used as a proxy.

Drug and IFI treatment costs. The economic evaluation of the BMT CTN 0101 trial data described here was conducted from the perspective of a health care provider and included direct health care costs only. The resources or events used for cost calculation included planned prophylaxis, supplemental prophylaxis, empirical antifungal therapy, and treatment of presumptive, probable, and proven IFIs. Resources used or events (i.e., supplemental prophylaxis, empirical therapy, and IFIs) were classified as occurring during the 6-month period if the resource use or event began less than 6 months from the planned prophylaxis start date. Similarly, a resource use or event was classified as occurring during the 12-month period if the resource use or event began within 12 months of the planned prophylaxis start date. Fungal infection-related resources used or events that started after 12

Table 1.
Clinical Trial Outcome Data Used in Modeling of Voriconazole and Fluconazole Prophylaxis^{a,b,c}

Variable	Voriconazole (n = 304)	Fluconazole (n = 295)
<i>6-Mo Outcomes</i>		
IFI category		
<i>Aspergillus</i> , probable or proven	9	17
<i>Candida</i> , probable or proven	3	3
Other/multiple, probable or proven	2	4
Presumptive	8	9
Total	22	33
Survival, %	81.2	80.0
Received empirical therapy, %	24.4	30.2
Received supplemental prophylaxis, %	31.9	19.0
<i>12-Mo Outcomes</i>		
IFI category		
<i>Aspergillus</i> , probable or proven	17	21
<i>Candida</i> , probable or proven	6	3
Other/multiple, probable or proven	7	7
Presumptive	8	10
Total	38	41
Survival, %	67.8	70.3
Received empirical therapy, %	24.7	30.5
Received supplemental prophylaxis, %	32.6	19.7

^aIFI = invasive fungal infection.

^bAll data are number of patients unless specified otherwise.

^cAdapted from table 2 in reference 5.

months were not collected in the clinical trial and therefore were not included in the cost-effectiveness analyses. The IFIs were classified into three groups: *Aspergillus*, *Candida*, and other.⁵ For the patients with two or more IFIs, all infections were considered for cost-calculation purposes. All costs are presented in 2011 U.S. dollars (Table 2).

The costs of proven or probable *Aspergillus*, *Candida*, and other IFIs were taken from the studies of Wilson and colleagues¹⁶ and Collins and colleagues¹³ and inflated to 2011 dollars using the medical price component of the Consumer Price Index. In the study of Wilson and colleagues,¹⁶ the Maryland Hospital Discharge Data Set and a case-control estimation method were used to estimate the incremental costs attributable to different types of IFI. Collins and colleagues¹³ used the values calculated by Wilson et al. for patients with

cancer, inflated to 2006 U.S. dollars, in their cost-effectiveness analysis. In the study reported here, the cost of presumptive IFIs was estimated as a weighted average of the cost of *Aspergillus*, *Candida*, and other IFIs, with weights derived from the relative frequency of the different types of probable or proven infections for each treatment group.

The cost of the planned prophylaxis regimen for each patient was estimated as the duration of the regimen (in days) multiplied by the cost of voriconazole or fluconazole per day according to age group (i.e., <12 and ≥12 years). The cost of supplemental prophylaxis or empirical therapy was estimated as the duration of therapy (in days) multiplied by the cost of therapy per day based on age group. The duration of supplemental prophylaxis or empirical therapy was determined as the earliest of the end date of therapy, the date of the onset

Table 2.
Costs of Treatment of Invasive Fungal Infections (IFIs) and Unit Costs of Antifungal Drugs¹³⁻¹⁵

Type of Therapy	Mean Cost (\$)
Treatment costs for presumptive, probable, and proven IFIs	
<i>Aspergillus</i> ^a	79,358
<i>Candida</i> ^a	29,419
Other ^a	15,001
Alternative treatment cost scenario ^b	48,011
Planned prophylaxis ^c	
Fluconazole, oral	
Patients <12 yr	7.11/day
Patients ≥12 yr	16.11/day
Voriconazole, oral; branded (generic)	
Patients <12 yr	67.31 (36.72)/day
Patients ≥12 yr	134.63 (73.44)/day
Empirical therapy ^{d,e}	
Amphotericin B, lipid formulation, i.v.	761.79/day
Caspofungin, i.v.	302.01/day
Fluconazole, i.v.	26.65/day
Itraconazole, i.v.	7.71/day
Micafungin, i.v.	93.50/day
Voriconazole, i.v.	149.54/day
Supplemental prophylaxis ^{e,f}	
Amphotericin B, lipid formulation, i.v.	756.19/day
Caspofungin, i.v.	307.24/day
Fluconazole, oral	15.59/day
Itraconazole, oral	20.89/day
Micafungin, i.v.	93.50/day
Voriconazole, oral; branded (generic)	128.59 (70.14)/day

^aCost estimates include incremental hospitalization costs for patients with cancer who developed IFI compared with patients with cancer without IFI, from Collins et al.¹³

^bAverage cost of treating all IFI types based on cost-effectiveness analysis of O'Sullivan et al.¹⁴ using 2004 Healthcare Cost and Utilization Project data on patients with blood cancers.

^cCosts based on dosing data from BMT CTN 0101 clinical trial protocol: 400 mg/day for patients ≥12 years of age, 200 mg/day for those <12 years of age and weighing ≥20 kg, 100 mg/day for those <12 years of age and weighing <20 kg; unit costs from *Red Book Online*.¹⁵

^dUse of i.v. formulation assumed; units costs from *Red Book Online*.¹⁵

^eFluconazole and voriconazole cost estimates derived from dosing data from BMT CTN 0101 clinical trial; for other drugs, estimates assume weighted-based dosing according to age, as recommended in prescribing information.

^fUse of oral formulation when possible assumed; units costs from *Red Book Online*.¹⁵

of fungal infection, or the end date of 12-month follow-up minus the start date of therapy plus one day. In two cases, the end date of supplemental prophylaxis therapy with fluconazole was not specified; in these cases, the duration was imputed as the average duration of supplemental fluconazole therapy among all patients who received it.

The dosing and unit costs assumed for each antifungal drug used by each trial participant were derived

as follows. For planned prophylaxis, the dosing was assumed to be that designated in the protocol, with fixed dosing for patients 12 years of age or older and weight-based dosing for those under 12 years of age; U.S. average weight values were used for patients under 12 years of age.¹⁷ The cost per milligram of therapy for the base-case analysis (fluconazole versus voriconazole prophylaxis) was estimated from the price for brand-name oral voriconazole and an av-

erage generic price for fluconazole using wholesale acquisition cost figures from *Red Book Online*.¹⁵ In a sensitivity analysis, the generic price for oral voriconazole, which was not available in the United States at the time of the study, was estimated based on data from *Red Book Online*.¹⁵ Costs per milligram were then converted into daily costs using the weighted average dose for the two treatment groups. Similar methods were used to estimate the daily costs of empirical therapy and supplemental prophylaxis from the BMT CTN trial data indicating which drugs were used for each patient receiving supplemental prophylaxis or empirical drug treatment. The trial data did not include information on the dosing or formulation of the drugs used.

We assumed that empirical therapy was always administered using an i.v. formulation and that supplemental prophylaxis was given orally unless the drug was not available in that formulation. We also assumed for both empirical therapy and supplemental prophylaxis that dosing was based on the prescribing information or, for voriconazole and fluconazole, the dose used for planned prophylaxis. In an alternative analysis, the generic price for oral voriconazole, obtained from *Red Book Online*, was used for all patients who took oral therapy.

Statistical analyses. The primary goal of the economic evaluation was to assess whether prophylaxis with voriconazole was cost-effective relative to prophylaxis with fluconazole based on the decision-tree diagram shown in Figure 1. Incremental cost-effectiveness ratios (ICERs), defined as the difference in average costs between the group of patients randomly assigned to receive voriconazole and the group assigned to fluconazole therapy divided by the difference in average outcomes for the two groups, were estimated. Outcomes used for the ICER estimates

included costs per IFI avoided and life-year gained.

Mathematically, the ICER pertaining to this study is given by the following equation:

$$ICER_{VF} = \frac{C_V - C_F}{E_V - E_F} = \frac{\Delta C_{VF}}{\Delta E_{VF}}$$

where ΔC_{VF} is the difference in the average cost ($C_V - C_F$) for the two prophylaxis groups (voriconazole [V] and fluconazole [F]) and ΔE_{VF} is the difference in the average effectiveness ($E_V - E_F$) of the two therapies. Voriconazole would be seen as cost-effective (i.e., a good value for the money) if $ICER_{VF} < R_C$, where R_C denotes the maximum willingness to pay (WTP) for an additional unit of effectiveness.

Due to uncertainty in determining R_C and in the estimation of $ICER_{VF}$, a probabilistic sensitivity analysis was conducted, with the results presented in the form of cost-effectiveness acceptability curves (CEACs)¹⁸ in Figure 2. The

CEAC depicts the probability that voriconazole is cost-effective for any value R_C . This method of presenting information on the uncertainty of the cost-effectiveness results is especially valuable when the differences between alternative treatments in costs or efficacy are small, as was the case with the efficacy differences analyzed in our study.

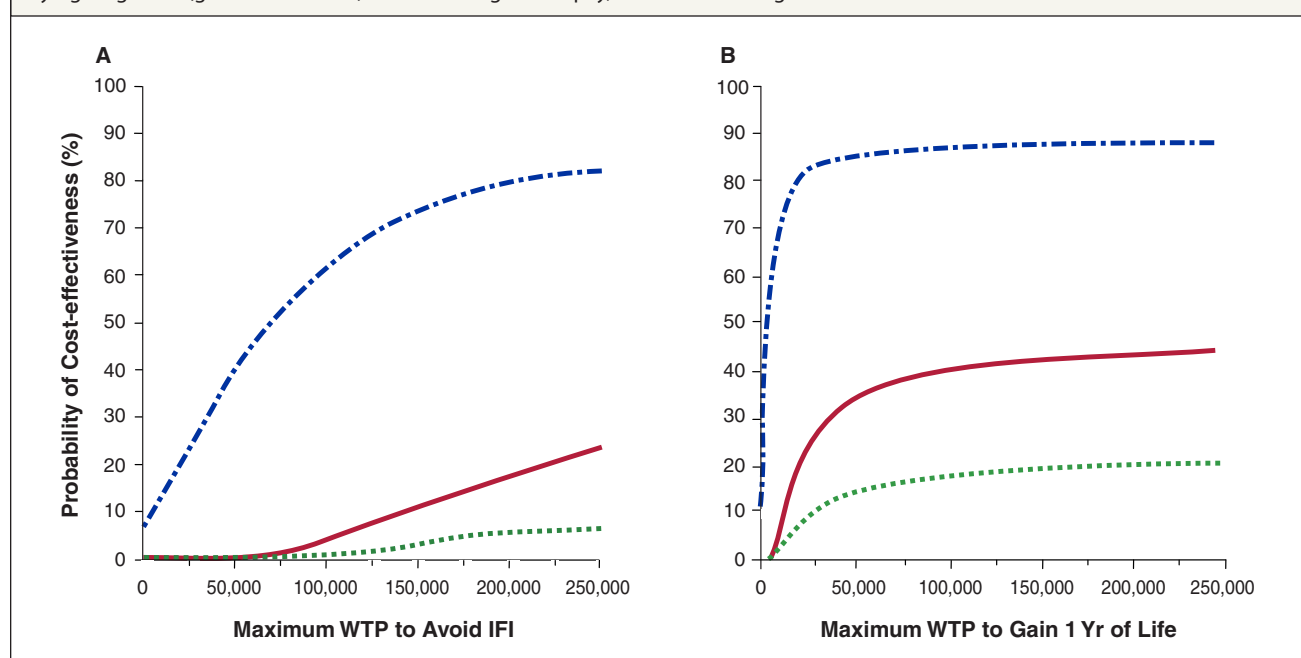
The economic analysis generated CEACs results for the overall study population and the two subpopulations using the net benefit associated with voriconazole versus fluconazole treatment (NB_{CVF}), expressed in units of money. The value NB_{CVF} is derived as follows:

$$NB_{CVF} = R_C(\Delta E_{VF}) - \Delta C_{VF} > 0$$

Using this equation, voriconazole was determined to be cost-effective if the calculated net benefits were positive (>0). A bootstrap method, with 1000 replications, was used to produce the CEACs in each population and for each efficacy measure.

In each bootstrap replication, we selected (with replacement) two random samples (i) of size n of cost-effect outcome pairs, one for clinical trial enrollees in the voriconazole group (n_{iV}) and one for those in the fluconazole group (n_{iF}), where n_{iV} and n_{iF} denote the original sample sizes of each treatment group in the population of interest. For each treatment group, we used the bootstrap resample to calculate the means, with 95% confidence intervals (CIs), for prophylaxis, empirical treatment, and IFI treatment costs and to calculate the values E_{iV} and E_{iF} , representing the drugs' effectiveness with regard to the clinical outcomes (i.e., IFI events and overall survival). The bootstrap 95% CIs were used instead of the parametric CIs due to the skewness of cost distributions. The means for each treatment arm were then used to calculate (1) the bootstrapped $ICER_{iVF}$ and (2) the bootstrapped net benefit statistic (NB_{iCVF}) for a range of values for R_C .

Figure 2. Results of base-case modeling of the probability of the voriconazole prophylaxis being cost-effective relative to fluconazole prophylaxis in reducing fungal infections (panel A) and extending expected life-years (panel B) in the total study population (red solid line), in a subgroup of patients with acute myeloid leukemia (blue dashed/dotted line), and in a subgroup of patients with other underlying diagnoses (green dotted line). WTP = willingness to pay, IFI = invasive fungal infection.



(i.e., the maximum WTP for an additional unit of effectiveness), where R_c ranged from \$50 to \$250,000 by \$50 increments. Finally, for each value of R_c , we calculated the proportion of times that the calculated net benefit was positive (i.e., $NB_{iCVF} > 0$). These proportions were plotted against their corresponding R_c values to produce each CEAC.

Results

Table 3 presents the mean costs and the two measures of benefit (i.e., IFIs avoided in the 12-month period after allogeneic HCT and life-years gained) for each treatment group, for the total trial population, and for the AML subgroup. Table 3 also presents the differences in mean costs and benefits between voriconazole and fluconazole. Mean total costs were significantly higher in the voriconazole prophylaxis group than in the fluconazole group at 12 months for the complete study population (i.e., the 95% CI did not contain zero) but were not significantly different for voriconazole and fluconazole in the AML subpopulation. At 12 months, costs other than those for planned prophylaxis were similar between

the two treatment groups (\$11,775 for voriconazole versus \$11,727 for fluconazole) for the complete study population, but these costs were lower for voriconazole (\$12,777) than for fluconazole (\$16,368) in the AML subpopulation.

Table 4 presents the cost-effectiveness estimates for cost per IFI avoided and cost per life-year gained for the base-case 6- and 12-month data and several alternative scenarios. In the 12-month base case, the cost per IFI avoided was found to be lower for the AML subgroup (\$66,919) than for the complete study population (\$812,990). Similarly, the cost per life-year gained was determined to be favorable for the AML subpopulation but unfavorable for the complete study population. The ICERs for the 12-month time period using oral voriconazole at the generic price instead of at the branded price were more favorable for generic voriconazole for both cost per IFI avoided and cost per life-year gained (\$9,683 versus \$66,919 and \$789 versus \$5,453, respectively) for the AML subpopulation (Table 4). For the AML subpopulation, the cost-effectiveness ratios (per IFI avoided)

for voriconazole in the 6-month base case were more favorable than those calculated using the 12-month data (\$34,576 versus \$66,919) because of the greater reduction in IFIs with voriconazole seen at 6 months than at 12 months.

The uncertainty associated with these estimated ICERs is presented using CEACs in Figure 2, which depicts the 12-month trial outcomes in the three populations examined (the study population, the AML subpopulation, and the “other-diagnosis” subpopulation). For every threshold value, the probability of voriconazole being cost-effective compared with fluconazole was much higher in the AML subpopulation than in the complete study population and in the other-diagnosis subpopulation. For example, the probability of voriconazole being cost-effective (per additional IFI) relative to fluconazole at a maximum WTP value of \$50,000 for each additional IFI avoided was 41% in the AML subpopulation, 0.4% in the complete study population, and 0.1% in the other-diagnosis subpopulation. Similarly, the probability of voriconazole being cost-effective (per life-year gained) rela-

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Table 3. Cost-effectiveness of Voriconazole Versus Fluconazole Prophylaxis: 12-Month Outcomes^a

Outcome	Total Study Population			AML Subgroup		
	Voriconazole	Fluconazole	Difference	Voriconazole	Fluconazole	Difference
<i>Clinical Outcomes</i>						
Mean IFI events per patient	0.127	0.137	-0.011	0.145	0.228	-0.083
Mean life-years	8.219	8.269	-0.05	7.911	6.891	1.020
<i>Cost of Therapy, \$^b</i>						
Planned prophylaxis	9,774	1,104	8,670 ^c	10,142	990	9,152 ^c
Other prophylaxis	3,162	1,165	1,997	2,809	897	1,911
Empirical therapy	1,744	2,284	-540	1,805	2,400	-595
IFI treatment	6,870	8,278	-1,408	8,164	13,070	-4,906
Total	21,549	12,831	8,718 ^c	22,919	17,358	5,562
<i>Incremental Cost-effectiveness Ratios</i>						
Cost per IFI avoided, \$ ^b	812,990			66,919		
Cost per life-year gained, \$ ^b	Dominated ^d			5,453		

^aAML = acute myeloid leukemia, IFI = invasive fungal infection.

^b2011 U.S. dollars.

^c95% confidence intervals estimated via bootstrap analysis did not include zero.

^dDenotes that treatment with voriconazole was both more expensive and resulted in fewer estimated life-years than treatment with fluconazole.

tive to fluconazole at a maximum WTP value of \$50,000 for an extra year of life was 85% in the AML subpopulation, 33% in the complete study population, and 15% in the other-diagnosis subpopulation.

Discussion

In this analysis, the costs and the cost-effectiveness of voriconazole compared with fluconazole have been estimated using data from the BMT CTN 0101 clinical trial⁵ in patients undergoing allogeneic HCT as well as published costs for antifungal drugs and for the treatment of IFIs. The analysis showed that at 12 months, mean total costs for the voriconazole prophylaxis group were significantly higher than for the fluconazole prophylaxis group for the complete study population and for the other-diagnosis subpopulation but were not significantly different for the AML subpopulation. Because of these differences, the cost per IFI avoided and the cost per life-year gained were also more favorable for the AML subgroup than for the complete trial population or the

other-diagnosis subpopulation. The cost per IFI avoided was more favorable at 6 months than at 12 months because of the smaller relative between-group difference in IFIs after 12 months. The cost-effectiveness ratios were all more favorable for voriconazole when the generic price for oral voriconazole was substituted for the branded price. The results of the bootstrap analyses, which reflect the uncertainty in the clinical trial results, showed that for the AML subpopulation, the probability of voriconazole being cost-effective was greater than 41% per avoided IFI and greater than 85% per life-year gained at a threshold of \$50,000.

The improved cost-effectiveness of voriconazole in the AML subpopulation relative to the total population may be related to the greater risk of developing IFIs in patients with AML. The Cox proportional hazards model applied in the BMT CTN 0101 study found that the AML subpopulation was at significantly greater risk for both death and IFI.⁵ As our cost analysis demonstrated that voriconazole may be more cost-effective for

the AML population than for the general population, one could consider that fluconazole may be more appropriate in the non-AML HCT population (patients with acute lymphoblastic leukemia, chronic myelogenous leukemia, myelodysplastic syndrome, or non-Hodgkin's lymphoma), in which the risks of IFI and of IFI-related mortality are lower.

In order to allow for health plans or hospitals to use the results presented here in situations where the distribution of patients among the underlying diseases or the costs of antifungal drugs or treatment of IFI differ from those assumed in our analysis, a model created using Office Excel (Microsoft Corporation, Redmond, WA) is available at the BMT CTN website (www.bmtctn.net). For example, wholesale acquisition costs were assumed for the drugs used for empirical therapy. If health plans or hospitals are able to obtain discounted prices for these drugs, the offsetting cost savings with voriconazole resulting from less need for empirical therapy will be reduced

Table 4.

Univariate Sensitivity Analysis for Cost-effectiveness Outcomes of Voriconazole Versus Fluconazole Prophylaxis^a

Scenario	Cost per IFI Avoided (\$ ^b)			Cost per Life-Year Gained (\$ ^b)		
	Total Study Population	AML Subgroup	Other-Diagnosis Subgroup ^c	Total Study Population	AML Subgroup	Other-Diagnosis Subgroup ^c
<i>12-Mo Outcomes</i>						
Base case	812,990	66,919	Dominated ^d	Dominated	5,453	Dominated
Generic oral voriconazole	384,099	9,683	Dominated	Dominated	789	Dominated
Alternative IFI treatment cost	881,219	71,210	Dominated	Dominated	5,802	Dominated
<i>6-Mo Outcomes</i>						
Base case	196,622	34,576	2,872,064	NA	NA	NA
Generic oral voriconazole	78,629	Dominant ^e	1,498,005	NA	NA	NA
Alternative IFI treatment cost	210,202	44,503	2,922,074	NA	NA	NA

^aAML = acute myeloid leukemia, IFI = invasive fungal infection, NA = not applicable.

^b2011 U.S. dollars.

^cPatients with underlying diagnoses other than AML.

^dDenotes that voriconazole therapy was both more expensive and resulted in fewer fungal infections avoided or fewer estimated life-years than fluconazole therapy.

^eDenotes that voriconazole therapy was both less expensive and resulted in more fungal infections avoided than fluconazole therapy.

relative to those calculated in our study. The impact of such price discounts can be estimated using the Excel model.

Several economic evaluations of antifungal prophylaxis in patients with hematologic malignancies have been performed for posaconazole or micafungin, although none have focused on patients undergoing allogeneic HCT. Six economic evaluations of posaconazole versus itraconazole or fluconazole were performed using data from a clinical trial of prophylaxis of up to 84 days in patients receiving intense chemotherapy for hematologic malignancies, with clinical endpoints determined at 100 days.^{14,19-22} The results of these studies all showed that posaconazole use was associated with cost savings and longer life expectancy relative to standard therapy with either itraconazole or fluconazole. A single-hospital observational cost-effectiveness analysis of data on patients undergoing induction chemotherapy for AML showed that switching from voriconazole to posaconazole resulted in cost savings and greater therapeutic success.²³ An economic evaluation using data from a 112-day clinical trial of posaconazole versus fluconazole prophylaxis in patients with graft-versus-host disease after allogeneic HCT showed increased costs and life expectancy with the use of posaconazole, resulting in an estimated cost per life-year gained of \$15,300.²⁴ In addition, two cost-effectiveness analyses of micafungin prophylaxis were performed using data from a clinical trial of patients undergoing HCT, 50% of whom received autologous transplants; in the trial, posttransplant prophylaxis was continued for up to 42 days, with outcomes assessed four weeks after the discontinuation of prophylaxis.^{25,26} Both studies found that micafungin prophylaxis was associated with lower total costs and fewer IFIs than fluconazole prophylaxis.

When the time horizon for the analysis presented in this article was shortened to 6 months, which is similar to the time horizons used in most previously published cost-effectiveness analyses of antifungal prophylaxis with posaconazole, micafungin, or voriconazole in patients with hematologic malignancies,^{13,14,19-23,25,26} the cost-effectiveness ratios were more favorable for voriconazole because the observed reduction in IFIs from 0 to 6 months was greater than the reduction from 0 to 12 months. In particular, for the AML subpopulation, the cost per IFI avoided was \$34,576 at 6 months compared with \$66,919 at 12 months. Whether a comparable attenuation of the benefit of antifungal prophylaxis would have been observed in the aforementioned clinical trials had they involved longer follow-up periods is unknown; however, if such attenuation had occurred, a similar unfavorable impact on cost-effectiveness ratios would have occurred in those studies.

The decision-analytic model used to derive the cost-effectiveness estimates had several limitations. The population included in the model base-case analyses was assumed to be similar to that included in the BMT CTN 0101 clinical trial. Also, the costs of adverse events associated with either voriconazole or fluconazole prophylaxis were not estimated because no significant differences in the occurrence of these adverse events were noted during the clinical trial.⁵ Moreover, costs for treating IFIs were derived from estimates for all patients with cancer rather than being limited to those with HCT, since data on the latter were not available. Also, it was assumed in the lifetime analysis of cost per life-year gained that no additional costs related to IFIs were incurred after the 12-month trial time period.

It is also possible that the increased costs with voriconazole compared with fluconazole might have

been overestimated, since we did not incorporate into our analyses the costs of adjunctive tests performed as part of a preemptive treatment strategy. For example, the voriconazole costs would be overestimated if galactomannan testing were routinely used for patients receiving fluconazole prophylaxis but not for those receiving voriconazole prophylaxis. Since galactomannan testing was performed routinely in both prophylaxis groups in the BMT CTN 0101 clinical trial, the impact on costs and outcomes of differential use of galactomannan testing between the prophylaxis groups could not be assessed. In addition, there may be utility in galactomannan screening in practice in patients taking voriconazole because, although the risk of aspergillosis is lower with voriconazole use, it does not disappear. This may be due in part to the known interpatient variability of blood levels of voriconazole.

Finally, the data for estimating expected life-years for the 12-month survivors according to age and underlying disease were incomplete; thus, assumptions were made based on available data. In particular, the relative risk of mortality in the second posttransplant year in comparison to general population mortality was assumed to be the same as that in the third year after transplantation. However, since this possible underestimate of mortality in the second year was applied to both prophylaxis groups and the difference in survival rates at 12 months was small, we believe the impact of this assumption on the difference in calculated life expectancy between the two groups was small.

Conclusion

The decision model indicated that voriconazole prophylaxis was cost-effective for patients undergoing allogeneic HCT for AML.

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