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Budget impact analysis of *CYP2C19*-guided voriconazole prophylaxis in AML

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Objectives: The objective of this study was to determine the economic impact of proactive, *CYP2C19* genotype-guided voriconazole prophylaxis in AML.

Methods: An Excel-based model was created to project the cost of treating a simulated cohort of severely neutropenic AML patients undergoing antifungal prophylaxis. The model compares (i) standard prophylactic dosing with voriconazole and (ii) *CYP2C19* genotyping of all AML patients to guide voriconazole dosing and prescribing.

Results: Based on the model, genotype-guided dosing of voriconazole conservatively spares 2.3 patients per year from invasive fungal infections. Implementing proactive genotyping of all AML patients in a simulated 100 patient cohort is expected to save a total of $41467 or $415 per patient.

Conclusions: The model, based on the robust literature of clinical and economic data, predicts that proactive genotype-guided voriconazole prophylaxis is likely to yield modest cost savings while improving patient outcomes. The primary driver of savings is the avoidance of expensive antifungal treatment and extended hospital stays, costing $30952 per patient, in patients succumbing to fungal infection.

Introduction

AML is a rapidly progressing cancer of the blood and bone marrow. Combination chemotherapy results in severe myelosuppression and immunosuppression, increasing patient risk of fungal infection.[1] Pharmacoeconomic studies suggest posaconazole is more cost-effective than voriconazole for antifungal prophylaxis in these patients.[2] However, voriconazole became available as a generic in 2010 and has rapidly declined in price compared with posaconazole, potentially increasing its attractiveness for antifungal prophylaxis.[3–5] In addition, recent data show cytochrome P450 enzyme CYP2C19 ultrarapid metabolizers (UMs) have increased clearance of voriconazole from the bloodstream resulting in subtherapeutic blood levels.[6–9]

Genotype-guided antifungal prophylaxis, either by increasing voriconazole dose or prescribing an alternative drug, for UMs could improve outcomes in these patients. Adequate prophylactic dosing of UMs should reduce the incidence of breakthrough fungal infections, reduce the likelihood of intolerance and potentially improve the cost-effectiveness of using voriconazole in immunocompromised AML patients. A budget impact analysis was performed to determine the expected costs or savings recognized by implementing a proactive genotyping strategy in a simulated cohort of 100 AML patients.

Methods

An Excel-based model (Microsoft® Excel® 2010 version 14.0, Microsoft Corporation, Redmond, WA, USA) was created to estimate the cost of treating a simulated cohort of 100 AML patients with (Scenario 1) standard prophylactic dosing with voriconazole or (Scenario 2) *CYP2C19* genotyping of all AML patients with UMs (*1/*17 and *17/*17) prescribed an increased dose of voriconazole with follow-up therapeutic drug monitoring (TDM). Both scenarios estimate costs associated with genotyping, prophylaxis and treatment of invasive fungal infections to predict overall costs/savings over a 1 year period. The model is based on the perspective of a third-party payer in the USA. Model parameters are detailed in Table 1.

The model assumes that 6.6 patients will develop an invasive fungal infection in Scenario 1 based on the incidence reported in Zabalza *et al.*[10] Scenario 2 assumes that 3.7 patients out of the 6.6 expected to develop a fungal infection are UMs and fail voriconazole prophylaxis because of underdosing (i.e. 56%×6.6 infections out of 100 patients=3.7 patients).[6] By increasing the initial dose of voriconazole, 2.3 patients can be spared from infection (i.e. 3.7 UMs×6.6% when adequately protected versus 3.7 UMs×17.5% when inadequately prophylaxed).[10,11] This will reduce the number of overall infections to 4.3 out of 100 patients, a rate

Table 1. Model parameters

Variable	Base case parameter	Source
Patient population	100	assumption
Incidence of fungal infection without prophylaxis	17.5%	11
Incidence of fungal infection with voriconazole prophylaxis	6.6%	10
Percentage of patients with low voriconazole trough levels due to CYP2C19 UM status	56%	6
Cost of *CYP2C19* genotyping assay	$291.80	18
Cost of voriconazole blood level	$18.68	18
Cost of one cycle of AML treatment without fungal infection	$44 752	13
Cost of one cycle of AML treatment with fungal infection	$75 704	13

closer to that of posaconazole, which does not suffer from underdosing issues due to metabolizer status.[12]

TDM of voriconazole blood levels is assumed to be performed on all UMs 5–7 days after the first dose of voriconazole. Sufficient data are not available to determine the number of UMs who will require dose escalation and a second blood test, so the model assumes 20%.

The cost per encounter of treating an AML patient who did not suffer an invasive fungal infection compared with one who did was determined to be US$44 752 and $75 704, respectively, for a marginal cost of $30 952.[13] Menzin *et al.*[14] reported a comparable amount of US$29 281 in 2009. Data from Rieger *et al.*[13] were converted into equivalent US$ in 2014 from euros in 2011 based on the average daily exchange rate for the year of publication, 2011, with cumulative inflation determined to be 5.4%.[15]

A one-way sensitivity analysis was performed to determine the impact of uncertainty on the model. Each model parameter was varied by ±20% to create a tornado plot.

Results

Based on the model, genotype-guided dosing of voriconazole for antifungal prophylaxis in neutropenic AML patients could conservatively spare 2.3 patients per year from invasive fungal infections (Table 2). Implementing proactive genotyping of all AML patients in a simulated 100 patient cohort is expected to save a total of $41 467 or $415 per patient. The primary driver of these savings is the avoidance of expensive treatment and extended hospital stays, costing $30 952 per patient, in patients succumbing to fungal infection.

A one-way sensitivity analysis was performed and cost savings dominated under all parameters (Figure S1, available as Supplementary data at *JAC* Online). The model is most sensitive to the incidence of fungal infection. A fungal infection rate <2% is the breakeven point where genotype-guided prophylaxis is not cost saving.

Table 2. Results of scenario analysis

Marginal costs	Events	Cost	Total
Screening all patients for *CYP2C19**17	100	($291.80)	($29 180)
Voriconazole level for UMs	36	($18.68)	($675)
		total	($29 803)
Marginal savings	**Events**	**Savings**	**Total**
Fungal infections avoided	2.3	$30 952	$71 270
		total	$71 270
Total savings			$41 467
Total savings per patient			$415

Discussion

This study is the first, to our knowledge, to estimate the budget impact of implementing proactive genotype-guided dosing of voriconazole as antifungal prophylaxis in AML patients. Given that more than a quarter of patients may be at risk of underdosing, genotype-guided prophylaxis is likely to reduce infections and improve outcomes in patients who otherwise would not have been adequately protected. Though modest at $415 saving per patient, the model robustly demonstrates that institutional adoption of pharmacogenomics can be cost saving to a payer.

Savings are likely to scale with larger patient volumes while improving patient outcomes by avoiding morbidity and mortality from invasive fungal infections. The findings are likely to be applicable to a number of scenarios where patients are given antifungal prophylaxis during severe neutropenia, e.g. ALL and bone marrow transplant. The model is extremely conservative in its assumptions and has the potential to yield increased savings in the event voriconazole efficacy can be improved by targeted dosing and is utilized as a less expensive alternative to posaconazole. The model could be reasonably applied to health systems similar to the US system. However, significant regional differences in healthcare costs such as drug prices and cost of inpatient stay as well as the allelic frequency of *CYP2C19**17 for a given population must be taken into account when translating the data to another setting.

Implementation of *CYP2C19* testing could have risks that should be considered. Because CYP enzymes metabolize a number of drugs, a question arises regarding the responsibility and potential liability of a healthcare provider to act on the patient's genotyping result in future, unrelated encounters or to educate patients about how the results could affect the efficacy or safety of drugs prescribed in the future. Managing this risk would require the investment of resources to both retain the genotyping information and prompt physicians when clinical decisions may be affected by the patient's genetics.

A lack of randomized, controlled trials for clinical utility and subsequent cost-effectiveness analysis of genomic medicine

has been noted by several experts in the field of personalized medicine.[16,17] As noted by these authors, pivotal trials and formal cost-effectiveness research is extremely resource intensive and costly. This model demonstrates that the impact of implementing personalized medicine can be reasonably estimated using the available data, validated by institutional knowledge and operational data, to support adoption of genetically targeted therapy to improve care and reduce costs. As these tests are implemented operationally, 'real-world' data should be collected, analysed and published to refine economic models and help further the practical and informed incorporation of genomic medicine into the clinic.

This model assumes a proactive approach to managing voriconazole dosing. TDM is another alternative to genotyping. At face value, TDM could be cheaper than upfront genotyping based on the costs of each assay. However, the kinetics of voriconazole require $\geq$5–7 days of dosing before an accurate steady-state blood level can be determined. UMs could thus be underdosed for $\geq$2 weeks before dose adjustments yield adequate prophylaxis, depending on the turnaround time of the assay. Avoiding one invasive fungal infection during this period by proactively genotyping patients would likely make this less costly than TDM from a total cost standpoint.

The budget impact analysis presented has a number of limitations and thus should be interpreted with caution. The model uses average cost of treatment and does not take into consideration patient-specific factors, number of treatment cycles, severity of disease, etc. Because the cost of treating AML and increase in cost due to treating invasive fungal infection are based on average costs (i.e. a mix of prophylactic drugs and treatment choices), costs associated with voriconazole dosing differences due to genotyping or switching to an alternative drug are not factored directly into the model.

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Transparency declarations

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Supplementary data

Figure S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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