Predicting Tolerance and Responses to BTK Inhibitors in CLL Patients with Treatment-Naïve or Relapsed/Refractory Disease Using Pharmacogenomics

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Background

Oral inhibitors of Bruton's tyrosine kinase (BTKi) are used for a number of B-cell malignancies, including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL) and Waldenstrom's macroglobulinemia/ lymphoplasmacytic lymphoma (WM/LPL). Despite excellent hematologic responses often seen with this class of medications, discontinuation is often indicated due to progression or intolerable side effects. Factors contributing to intolerance are not fully understood. With regards to discontinuation due to progression, mechanisms of resistance besides mutations in BTK and PLCγ are not well characterized. Prior work has suggested the role of cytochrome P450 polymorphisms in increasing the risk of targeted therapy discontinuation in CLL. We therefore analyzed pharmacogenomic testing in Veterans treated with BTKi to evaluate the extent to which CYP polymorphisms affect intolerance and responses to BTKi therapy.

Methods

We identified Veterans diagnosed with chronic lymphocytic leukemia (CLL) receiving care through the Veterans Administration (VA) who were prescribed BTKi and had undergone pharmacogenomic testing through the Pharmacogenomic Testing for Veterans (PHASER) program, currently offered to veterans at 22 VA facilities across the United States. We retrospectively analyzed clinical factors including time on BTKi therapy, reasons for temporary or permanent discontinuation or dose changes, medical comorbidities, and grade of pertinent side effects associated with BTKi (arrhythmia, hypertension, bleeding, fatigue, arthralgias, rash, diarrhea) as well as use of concomitant medications known to interact with CYP2C or CYP2D6, the major cytochrome P450 enzymes involved in the metabolism of BTKi.

Demographics

Table 1. Overview of patient demographics.

Total Number of Patients	77
Gender	
M	74 (96%)
F	3
BTKi	
Ibrutinib	67 (87%)
Acalabrutinib	8
Zanubrutinib	5
More than 1 BTKi	6
Line of Therapy	
1L (ibrutinib)	42
1L (acalabrutinib)	16
2L (ibrutinib)	13
2L (acalabrutinib)	6
Median age at starting BTKi (y)	71.2 (47.7-95.7)
Median time on BTKi (m)	27.5 (0.5-91.7)
Progression on BTKi	11(14%)
Intolerance on BTKi	26 (34%)
Temporary Discontinuation of BTKi	26 (34%)
Concurrent use of anticoagulation	13 (14%)

Concomitant Medications of Interest

Table 2. Strong inhibitors of cytochrome P450 enzymes.

CYP2C9	CYP2C19	CYP2D6
Amiodarone	Esomeprazole	Abiraterone
Fluconazole	Fluconazole	Bupropion
Metronidazole	Fluoxetine	Cinacalcet
Phenylbutazone	Fluvoxamine	Doxepin
	Ketoconazole	Duloxetine
	Omeprazole	Fluoxetine
	Ticlopidine	Terbinafine
	Voriconazole	Paroxetine

Intolerance to BTKi is Associated with CYP2C19 and CYP2D6 Poor Metabolizer Phenotypes in Previously Untreated CLL

In our cohort, 58 patients initiated ibrutinib or acalabrutinib as monotherapy for previously untreated CLL. CYP2D6 poor metabolizer phenotype (due to genotype and/or concomitant medications) associated with shorter time to discontinuation of BTKi due to intolerance (Figure 1a), while CYP2C19 poor metabolizer phenotype associated with shorter time to discontinuation due to progression on BTKi (Figure 1b).

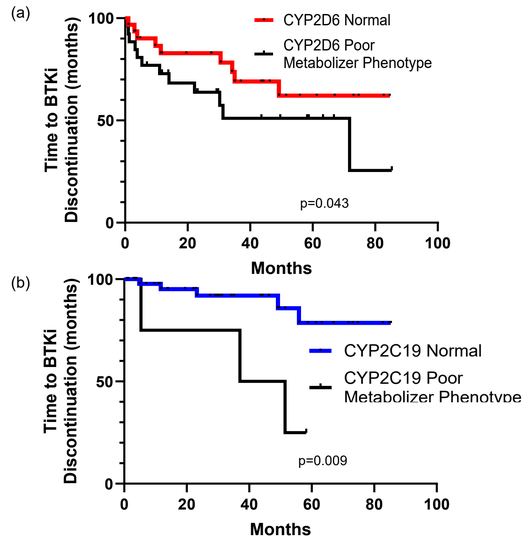

Figure 1. (a) BTKi time to discontinuation in CLL patients due to intolerance based on CYP2D6 metabolizer phenotype. (b) BTKi time to discontinuation in CLL patients due to progression based on CYP2C19 metabolizer phenotype.

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CYP2D6 Poor Metabolizer Phenotypes Predict Progression in Relapsed/Refractory CLL Patients on BTKi

In our cohort, we identified 19 patients with relapsed/refractory CLL who were prescribed BTKi. CYP2D6 (Figure 2a), but not CYP2C19 (Figure 2b), poor metabolizer phenotypes predicted shorter time to BTKi discontinuation due to disease progression.

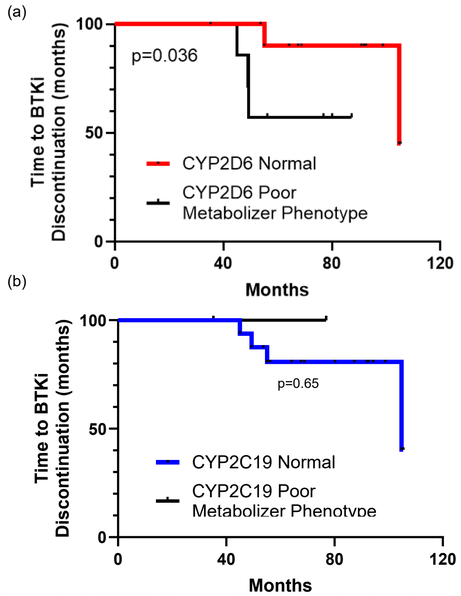

Figure 2. (a) BTKi time to discontinuation in relapsed/refractory (r/r) CLL patients due to progression based on CYP2D6 metabolizer phenotype. (b) BTKi time to discontinuation in r/r CLL patients due to progression based on CYP2C19 metabolizer phenotype.

Conclusions

CYP2D6 poor metabolizer phenotypes associated with BTKi intolerance, warranting consideration of minor contributors to metabolism when considering maximum tolerated doses. Genotypes predicting impaired metabolism through multiple CYP genes, both directly related and unrelated to BTKi metabolism, paradoxically associated with worse EFS due to progression despite the presumed higher BTKi bioavailability. Future investigation will include consideration of concomitant drugs which may contribute to or counterbalance predicted phenoconversion based on pharmacogenomic analysis.