Comparative outcomes of patients newly initiating first-generation vs. second-generation tyrosine kinase inhibitors for chronic myeloid leukemia

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Background

- Imatinib, a first-generation tyrosine kinase inhibitor (1GTKI), and nilotinib and dasatinib, two second-generation TKIs (2GTKI), are FDA approved as first-line therapy for chronic myeloid leukemia (CML). Guidelines recommend first-line therapy with any of these agents, but no consensus exists for determining which agent should be used first.
- In clinical trials, 2GTKIs as first-line therapy had higher rates of responses (complete cytogenic response [CCyR] and major molecular response [MMR]) and lower likelihood of progression to accelerated phase or blast crisis, with improved overall survival compared to imatinib.[1-6] However, approximately 2/3 of patients will have an acceptable response to first-line therapy with imatinib.[7]
- Adherence and costs are important factors in treatment selection, as adherence is positively correlated with survival-related endpoints,[8-10] and the cost of a 1-year supply ranges from $80,000 to $90,000 for imatinib and up to $124,000 for dasatinib and nilotinib.[11] Patients often are responsible for a 20% copay on these medications.
- No comparative studies have been conducted on first and second-generation TKIs outcomes in a real world setting.

Objective

- To examine the association between patients newly initiating a TKI (1GTKI vs. 2GTKI) and the following outcomes: treatment patterns, medication adherence, health services utilization, and direct health care costs.

Methods

Study design: Retrospective, observational cohort study **(Figure 1)**

Data source: Pharmacy and medical claims, and enrollment data, from the Humana Research database

Methods, cont.

Inclusion and exclusion criteria:

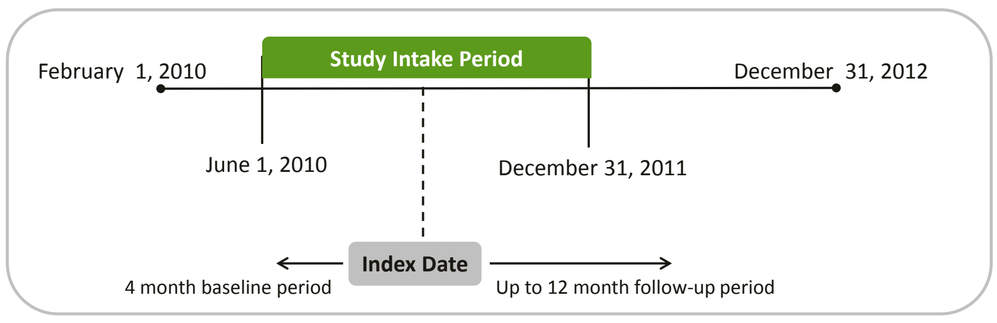
- Patients newly initiating a 1GTKI or 2GTKI therapy for diagnosed CML during the study intake period, June 1, 2010 and December 31, 2011.
- Continuous enrollment in a Humana plan with prescription drug coverage during the 4-month baseline period.
- Age 18-89 at time of initial TKI pharmacy claim (index date), and no TKI pharmacy claim during 4-month baseline period.
- For health service and cost outcomes: Enrolled in a Humana plan that provides both pharmacy and medical coverage (i.e., fully-insured commercial and Medicare Advantage) and 12 months of follow-up.

Outcomes and Statistical Analyses:

- Treatment patterns included treatment interruptions, time to treatment interruptions, and regimen changes. Treatment patterns were compared using multivariable Cox proportional hazard regression models.
  - *Treatment interruption:* gap in any TKI pharmacy claim longer than an allowable refill gap plus days' supply from the previous TKI pharmacy claim
  - *Regimen change:* either a pharmacy claim for a different TKI therapy, or a dose increase for the same medication
- Medication adherence was defined as the proportion of days covered, with ≥0.85 being classified as adherent. Multivariate logistic regression was used to examine the association between TKI therapies and medication adherence.
- Health service utilization included the number of outpatient visits, inpatient admissions, emergency room visits, and mean hospital days, and were compared using multivariate logistic regression and generalized linear models (GLM).
- Direct health care costs were the sum of plan and patient paid during the 12-month follow-up period. Predicted costs were compared using GLM with gamma distribution and log link function.
- Covariates used in the statistical models included: age, gender, plan type, region, low income subsidy, dual eligibility status, RxRisk-V score, phase of CML disease using starting dose of TKI as a proxy, flu or pneumonia vaccination, medication count, and provider characteristics (age, gender, specialty, provider practice setting).

Results

Figure 1. Study Design



The index date was defined as the first pharmacy claim for imatinib, nilotinib, or dasatinib during the study intake period. A 4 month baseline period with no pharmacy claims for TKI therapy prior to the index date was used to define an incident user of a TKI. Patients were followed for up to 12 months after the index date, which was defined as the follow-up period.

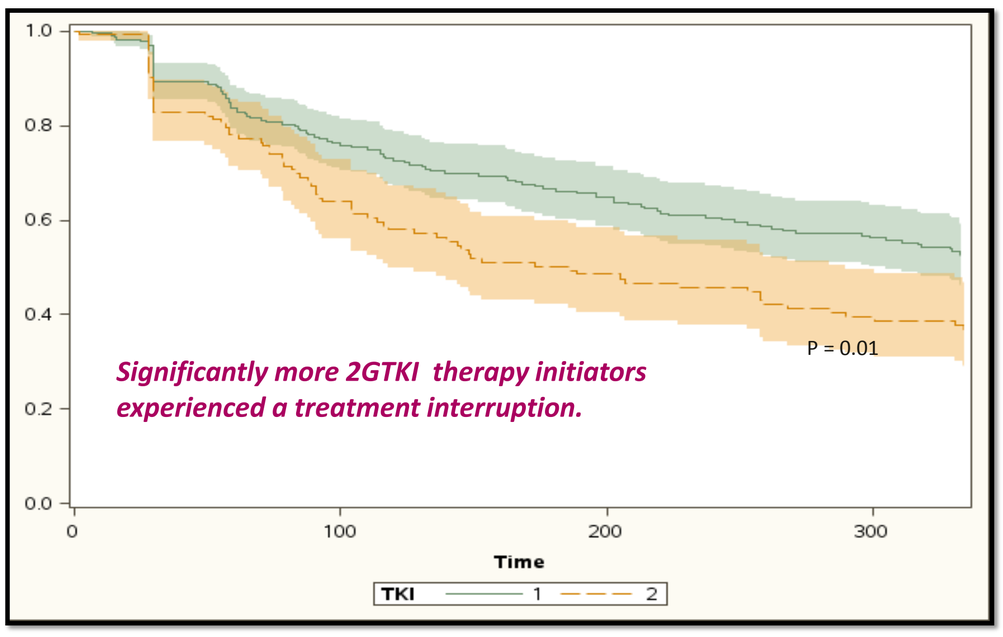
Table 1. Sample Characteristics

- More patients initiating therapy with a 2GTKI were younger, covered by commercial insurance, and using TKI doses consistent with accelerated or blast crisis phase of CML.

	1GTKI n=237	2GTKI n=131	P-value
Age in years, mean (SD)	69.9 (11.4)	67.2 (13.5)	0.04
Female, n (%)	125 (52.7%)	74 (56.5%)	0.49
Plan type, n (%)			
Commercial fully-insured	14 (5.9%)	17 (13.0%)	0.04
Medicare Advantage	94 (39.7%)	37 (28.2%)	
Medicare PDP	129 (54.4%)	77 (58.8%)	
Geographic region, n (%)			
Northeast	15 (6.3%)	13 (9.9%)	0.56
Midwest	50 (21.1%)	29 (22.1%)	
South	134 (56.5%)	72 (55.0%)	
West	38 (16.1%)	17 (13.0%)	
Low income subsidy, n (%)*	54 (22.8%)	36 (27.5%)	0.32
Proxy for CML phase, n (%)†			
Chronic	230 (97.0%)	108 (82.4%)	<0.0001
Accelerated or blast crisis	7 (3.0%)	23 (17.6%)	
>2 unique concurrent medications‡, n (%)	133 (56.1%)	72 (55.0%)	0.83
Patient out-of-pocket cost for index medication, mean (SD)	$1,566 ($1,204)	$1,844 ($1,586)	0.12
RxRisk-V Scores, mean (SD)	5.1 (3.3)	5.0 (3.1)	0.69
Oncologist provider, n (%)	221 (93.3%)	122 (93.1%)	0.97

** Low income subsidy only assessed for patients insured by Medicare*
† Patients' starting dose of TKI therapy was assessed and used as a proxy for CML phase at the time of initiation
‡ Count of all medications with the exception of TKI therapies. Required two or more claims to eliminate including medications for short term use.
§ Determined based on the identification of 45 distinct comorbid conditions via their associated medication treatments. A higher score indicates a higher chronic disease burden.

Figure 2. Time to Treatment Interruption (days)



- After adjusting for covariates, patients receiving a 2GTKI had a 48% higher risk of treatment interruption vs. patients receiving a 1GTKI (hazard ratio 1.48, 95% confidence interval [CI] 1.08-2.02).
- Approximately 19% of patients had a regimen change, but there were no differences in rates of regimen changes between the two generations.

Medication Adherence by TKI Treatment Group

- After adjusting for covariates using multivariable logistic regression, the proportion of adherent patients did not differ between patients initiating a 1GTKI compared to a 2GTKI (odds ratio [OR]=0.88, 95% CI 0.55-1.40).

Health Services Utilization by TKI Treatment Group

- Outpatient visits were the most frequently used health service in both treatment groups (1GTKI=37.8 visits, 2GTKI=42.3 visits). After adjustment, the 2GTKI cohort utilized outpatient visits more than the 1GTKI cohort (incident rate ratio [IRR]= 1.12, 95% CI 1.06-1.2).
- Although there was no association between initiating a 1GTKI and 2GTKI and inpatient admissions (OR=3.91, 95% CI 0.91-16.76), initiating a 2GTKI was associated with increased inpatient days compared to initiating a 1GTKI (IRR=3.25, 95% CI 2.43-4.35).
- The annual mean number of emergency room (ER) visits was less than 1 in both groups and was not statistically different between groups.

Table 2. Direct Health Care Costs (Plan + Patient Paid) by TKI Treatment Group

Total costs were significantly higher among 2GTKI initiators.

Pharmacy costs were 1.3 times higher in the 2GTKI group compared to the 1GTKI group.

	1GTKI, n=91 Mean (95% CI)	2GTKI, n=42 Mean (95% CI)	P-value
Total costs*	$66,443 ($61,194 - $72,143)	$86,509 ($76,275 - $98,125)	0.001
TKI pharmacy costs	$51,344 ($47,014 - $56,072)	$64,991 ($56,818 - $74,340)	<0.01
Non-TKI pharmacy costs	$1,387 ($1,064 - $1,807)	$2,294 ($1,480 - $3,556)	0.09
Medical costs	$9,331 ($7,389 - $11,783)	$12,633 ($8,691 - $18,365)	0.22

**Total cost is a predicted value inclusive of medical costs, TKI pharmacy costs, and non-TKI pharmacy costs. Because it is a predicted cost, the total cost is not the arithmetic sum of the three component costs.*

Conclusions and Implications

- Both treatment interruptions and outpatient visits were significantly more common among patients initiating therapy with a 2GTKI.
- However, there were no differences in regimen changes, medication adherence, inpatient hospitalization, ER visits, or medical costs among patients newly initiating a 1GTKI vs. 2GTKI.
- Patients initiating a 2GTKI incurred significantly higher total costs and TKI pharmacy costs than patients initiating a 1GTKI.
- With the impending release of generic imatinib, cost differences between 1GTKI and 2GTKI is expected to increase.
- These data can assist health care providers in choosing the most appropriate initial TKI therapy for each patient.
- Future research should evaluate comparative clinical outcomes for 1GTKI and 2GTKI in a real world setting, as well as the ideal sequencing strategy for these agents..

Limitations

- Although the statistical models controlled for a number of potential confounders, residual confounding due to unmeasured and inadequately measured confounders cannot be ruled out.
- Common limitations of administrative claims data, such as errors in claims coding and missing data, apply to this study.
- CML phase was not available in the data, so the starting dose of the index medication was used as a proxy.
- Laboratory results were not available; therefore, clinical outcomes such as complete cytogenetic response (CCyR), major molecular response (MMR), and disease progression could not be assessed or accounted for.

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