Spring 5-2019

How Patient Cost Sharing Affects Tyrosine Kinase Inhibitors Adherence And Outcomes Among Commercially Insured Patients With Newly Diagnosed Chronic Myeloid Leukemia

Hsiao Ling Phuar
UTHealth School of Public Health

HOW PATIENT COST SHARING AFFECTS TYROSINE KINASE INHIBITORS ADHERENCE AND OUTCOMES AMONG COMMERCIALLY INSURED PATIENTS WITH NEWLY DIAGNOSED CHRONIC MYELOID LEUKEMIA

by

HSIAO LING PHUAR, MSC, BPHARM

APPROVED:

CHARLES E. BEGLEY, PHD

WENYAW CHAN, PHD

TRUDY MILLARD KRAUSE, DRPH, MBA

DEAN, THE UNIVERSITY OF TEXAS
SCHOOL OF PUBLIC HEALTH

DEDICATION

To my family

HOW PATIENT COST SHARING AFFECTS TYROSINE KINASE INHIBITORS ADHERENCE AND OUTCOMES AMONG COMMERCIALLY INSURED PATIENTS WITH NEWLY DIAGNOSED CHRONIC MYELOID LEUKEMIA

by

HSIAO LING PHUAR

BPHARM, Universiti Sains Malaysia, 2006
MSC, The London School of Economics and Political Science, 2012
MSC, London School of Hygiene & Tropical Medicine, 2012

Presented to the Faculty of The University of Texas

School of Public Health

in Partial Fulfillment

of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

THE UNIVERSITY OF TEXAS
SCHOOL OF PUBLIC HEALTH
Houston, Texas
May, 2019

PREFACE

I am a Fulbright scholar and registered pharmacist from Malaysia who came to the United States to study healthcare management and health policy. I work at the Ministry of Health Malaysia where I was involved with the national medicines policy and healthcare reform initiative prior to starting my PhD program. I am interested in cancer health disparities, which is a global public health problem. This is in part due to more people surviving cancer as a result of advancement in treatment technology and pharmaceutical discoveries that comes with increasing financial burden. I am particularly interested in further understanding current disparities in access to and quality of cancer care, and learning about the medical financial hardship among cancer survivors. My future aim is to effectively engage with pharmaceutical stakeholders in the public and private sectors to establish an affordable and sustainable financing mechanism to achieve universal access to medicines.

ACKNOWLEDGEMENTS

I am deeply grateful to Dr. Charles Begley for his mentorship and guidance throughout my time at The University of Texas Health Science Center at Houston School of Public Health. I want to also thank Drs. Wenyaw Chan and Trudy Millard Krause for their assistance and advice on my dissertation work. And as always, I am thankful to my family and friends for their encouragement and support that made everything possible.

Support for my doctoral studies was provided by the Fulbright scholarship and study leave granted by the Ministry of Health Malaysia.

HOW PATIENT COST SHARING AFFECTS TYROSINE KINASE INHIBITORS ADHERENCE AND OUTCOMES AMONG COMMERCIALLY INSURED PATIENTS WITH NEWLY DIAGNOSED CHRONIC MYELOID LEUKEMIA

Hsiao Ling Phuar, MSc, BPharm, PhD
The University of Texas
School of Public Health, 2019

Dissertation Chair: Charles E. Begley, PhD

Untreated chronic phase chronic myeloid leukemia (CML) will eventually progress to advanced phase in 3 to 5 years. Treating CML with tyrosine kinase inhibitors (TKIs) has turned it into a chronic, manageable disease where most patients experience near normal life expectancy, particularly those diagnosed before age 65 years. Patients are required to continuously take their oral TKIs daily to produce the anticipated benefit of long-term survival. High out-of-pocket costs may lead to disparities in the initiation of and subsequent adherence to these expensive TKIs. Therefore, the goal of this dissertation is to assess the relationship between patient prescription cost sharing, TKIs initiation and adherence, and healthcare utilization and costs in a large group of commercially insured patients with newly diagnosed CML. The objective is twofold: 1) determine how patient cost sharing of TKI affects initiation, and healthcare utilization and costs, and 2) examine the association between TKI out-of-pocket costs, adherence, and healthcare utilization

and costs. For these two objectives, we conducted a retrospective cohort study using longitudinal medical and pharmacy claims data from IBM® MarketScan® Commercial Database from 2011 to 2015. We included patients who were recently diagnosed with CML and filled at least one prescription for TKI. We found that high out-of-pocket costs for TKI medications put patients at increased risk of non-adherence. Patients with early initiation of TKI and better adherence had higher TKI medication costs, but experienced fewer hospitalizations, resulting in lower medical and total annual healthcare costs. In summary, our findings suggest that high drug out-of-pocket costs may limit access to life-saving oral anticancer medications, causing disparities in TKI initiation and adherence for CML treatment. Oral anticancer medications are typically covered under a pharmacy benefit with substantial out-of-pocket costs due at the time the medication is obtained at the pharmacy. Efforts to lower drug prices and subsequently, the out-of-pocket costs for TKI medications could significantly improve adherence, and overall health and economic outcomes among CML patients.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

BACKGROUND

Literature Review

Cancer and Targeted Therapies

In the United States, cancer comes in second among all causes of death after heart disease. [1] However, the 5-year relative survival rate for all cancers diagnosed between 2004 and 2010 was 68%, an improvement from 49% three decades before, which reflects earlier diagnosis of certain cancers and advancement in treatment technology. [2] There are more Americans surviving cancer over a 10-year period with current statistics showing approximately 15.5 million cancer survivors in January 2016 [3] in comparison to 11.4 million in January 2006 [4]. The Agency for Healthcare Research and Quality (AHRQ) estimated that the direct medical costs for cancer in the United States were $88.7 billion in 2011 with 11% being spent on prescription drugs. [2] Between 2010 and 2020, national costs of cancer care were projected to increase 27% from $125 billion to $158 billion with only growth and aging in population accounting for this increase in costs, but if incidence, survival, and cost trends were also taken into account, the projected 2020 costs could go as high as $173 billion, showing a 39% increase instead. [5]

Much anticancer drug development has focused on targeted therapies. [6] The use of targeted therapies in cancer grew from 11% in 2003 to 46% in 2013 [7] because additional indications for such drugs approved in the early 2000's led to their increased uptake, affecting the use of traditional cytotoxic and hormonal

therapies [8]. Targeted cancer therapies inhibit molecular targets involved in the growth, progression, and spread of cancer [6]. Chronic myeloid leukemia (CML) cells contain a *BCR-ABL* oncogene not found in normal cells, which makes a BCR-ABL protein that causes CML cells to grow and reproduce unchecked. [9] This type of protein is known as a tyrosine kinase, and the standard treatment for CML is tyrosine kinase inhibitors (TKIs), drugs that target BCR-ABL. [9]

Chronic Myeloid Leukemia and Tyrosine Kinase Inhibitors

CML accounts for 15% of adult leukemias. [10] The median age at diagnosis is 65 years; however, CML occurs in all age groups with 47.7% of new cases diagnosed among people aged 20-64. [11] In 2018, an estimated 8,430 people are expected to be diagnosed with CML in the United States, and 1,090 people are expected to die from the disease. [11]

CML occurs in three different phases (chronic, accelerated, and blast phase), and is usually diagnosed in the chronic phase. [10] Untreated chronic phase CML will eventually progress to advanced phase in 3 to 5 years. [12] Imatinib, dasatinib, and nilotinib are recommended as first-line TKI therapy for newly diagnosed patients with chronic phase CML, followed by bosutinib and ponatinib as second line options. [10,13,14] Imatinib [Gleevec, Novartis], was the first TKI approved by the US Food and Drug Administration (FDA) for CML treatment in 2001, followed by dasatinib [Sprycel, Bristol-Myers Squibb] in 2006, nilotinib [Tasigna, Novartis] in 2007, and bosutinib [Bosulif, Pfizer] and ponatinib [Iclusig, Ariad Pharmaceuticals] in 2012. [15]

TKIs are considered to be the most successful class of targeted cancer therapies, exceeding all survival expectations. [16] Before TKIs, a stem cell transplant was considered the treatment of choice for CML, but this complicated treatment can cause serious side effects [17], and is no longer recommended as the first-line option for patients with chronic phase CML [10]. TKIs play a large part in more than doubling the 5-year survival rate for CML over the past two decades, from 31% for patients diagnosed in the early 1990's to 66% for those diagnosed from 2006 to 2012 [3]. The median survival used to be 4 to 6 years, but today most CML patients treated with TKIs experience near normal life expectancy, particularly those diagnosed before age 65 years. [18,19]

Treating CML with TKIs has differentiated the condition from solid cancers, such as sarcomas, carcinomas, or lymphomas, turning it into a chronic, manageable disease similar to diabetes, hypertension, and cardiovascular disorders. [13,16] Patients are required to continuously take their oral TKIs daily to produce the anticipated benefit of long-term survival. Despite significant clinical benefits, several studies employing a variety of methods for measuring patient adherence have demonstrated 10-98% adherence to approved TKIs. [20-27] Non-adherent patients not only get fewer therapy benefits, but they also face risk of treatment failure due to resistant CML. [21,23]

Economic Burden of Chronic Myeloid Leukemia

Much attention has been focused on the high cost of TKIs and whether these

costs inhibit patient use. [16] Anticancer drug prices have more than doubled from an average of $5,000 per month a decade ago to more than $10,000 per month. [16] Imatinib was initially priced at nearly $30,000 per year when it was released in 2001, and its price tripled to $92,000 per year in 2012. [16] Imatinib, as one of the most successful targeted cancer therapies, may have paved the way for the rising cost of anticancer drugs. [16] Bosutinib and ponatinib, both introduced in 2012, were priced at $118,000 and $138,000 per year respectively. [16] These estimates are based on average wholesale prices, however, and would not be actual prices paid by patients with health insurance coverage. [28]

People with health insurance have a better chance of surviving cancer than people who are uninsured. Newly diagnosed CML patients in the United States who were uninsured or had Medicaid were associated with worse 5-year overall survival in comparison with being insured. [29] Having prescription drug coverage is an important determinant for cost-related medication non-adherence. [30] Prescription drug coverage protects the patients from having to pay the full price of a drug out-of-pocket. Even so, the financial protection by prescription drug coverage differed considerably by source of coverage with rates of out-of-pocket cost-related medication non-adherence ranging from 9% if patients had the Veterans Affairs drug coverage to 18% with private insurance, 25% with Medicare, and 31% with Medicaid. [31]

In order to control costs, prescription drug plans in the United States tend to

have cost-sharing mechanisms that can result in patients initiating anticancer drugs facing high out-of-pocket costs. [32] Cost-sharing mechanisms such as higher copayment amounts, co-insurance, or annual deductibles [33-35] shift the financial risks of the high-cost drugs from the plan to the patients, which then can cause them to become non-adherent to their cancer treatment [36]. Cost sharing has reduced outpatient prescription drug spending growth from 16% in 2000 to 8% in 2004. [37]

Increased cost sharing reduces prescription medication use. [30,38] To reduce out-of-pocket costs, patients may choose not to fill the prescription ("primary" non-adherence), or split pills, skip doses, or delay refills ("secondary" non-adherence). [39] Every 10% increase in cost sharing decreases patients' prescription drug spending by 2 to 6%. [38] About 20-35% of cancer patients delay, forgo, or modify treatments because of high out-of-pocket costs, affecting survival rates. [40] Higher out-of-pocket drug costs (≥$30 per prescription) were associated with non-adherence in patients taking oral anticancer drugs. [41-43] Chronically ill patients with monthly out-of-pocket drug costs exceeding $100 were five times more likely to be non-adherent compared to those with costs below $50. [44] A retrospective analysis of claims data from over 10,000 patients taking oral anticancer drugs, including imatinib, reported that 10% of patients abandoned a newly prescribed oral cancer therapy due to higher patient cost sharing. [33]

Because non-adherence is a common issue, the National Comprehensive Cancer Network (NCCN) CML guidelines recommend that when patients fail to

achieve optimal response at specific milestones as early as 3 months, physicians should first assess patient TKI adherence before making any treatment adjustments. [10] Hematologic [normalization of peripheral blood counts], cytogenetic [decrease in the number of Philadelphia-positive metaphases using bone marrow cytogenetics], and molecular [decrease in the amount of BCR-ABL1 chimeric mRNA using quantitative reverse transcriptase polymerase chain reaction, (QPCR)] responses are measured to assess response to TKI treatment. [10]

The goal of TKI therapy is to achieve a complete cytogenetic response (CCyR) within 12 months of therapy initiation and to prevent disease progression to accelerated or blast phase. [10] Hence, adherence to oral TKI therapy is crucial. Adherent patients have better early responses and long-term outcomes with TKI therapy. [13] Patients taking less than the prescribed medication or having treatment gaps can fail to achieve CCyR, major molecular response (MMR), and complete molecular response (CMR). [45] Even when patients miss as little as 10% of their daily doses, amounting to as few as 3 days per month, they end up being less likely to achieve MMR and more likely to lose cytogenetic response. [20,21,23,46]

The success story of TKIs shows how effective but expensive novel anticancer drugs will continue improving patient outcomes and expanding treatment options, but patients and insurers are left to bear the increasing financial burden. [47] Despite their high cost, optimal use of TKIs has generated substantial health improvements for CML patients, and can reduce the economic burden of CML for

insurers through decreased healthcare utilization.[47-50]

Public Health Significance

Medication adherence, defined as "the process by which patients take their medication as prescribed", can be further divided into three quantifiable phases: (1) initiation, (2) implementation, and (3) discontinuation.[51,52] Non-adherent patients may delay or not initiate prescribed treatment (Phase 1), or compromise dosing regimen or treatment duration (Phases 2 and 3). Medication adherence can be affected by various inherently related factors that have critical therapeutic and health implications.[52] Due to the high costs of TKIs, it is relevant to study if demand for these drugs is affected by the cost-sharing burden imposed on patients by insurance benefit design. Benefit-design decisions regarding anticancer drugs are particularly challenging given the severity of the illnesses they treat, and insurers having to balance the need to ensure patient access to a wide range of treatment options and the need to control healthcare spending.[47]

This dissertation adds to existing literature by studying CML patients prescribed with TKIs using administrative claims data collected from individuals insured through commercial employer health insurance plans. This study provides insight into the impact of expected out-of-pocket spending on TKI initiation and implementation (popularly termed as "adherence" and will subsequently be referred to as such), the first two phases of "medication adherence" described previously that are expected to bring the most benefit for adherent patients. Most medication

adherence studies evaluated use among patients who had initiated therapy, and not so much on factors associated with therapy initiation itself. Two studies that examined factors associated with TKI initiation and adherence were done in a population of Medicare beneficiaries. [53,54] Another study that examined cost sharing and TKI adherence in a commercially insured population used TKI claims from 2002 to 2011. [28] This dissertation used available data of five years from 2011 to 2015 that enabled the study of the five TKIs currently approved for treatment of CML. In addition, the study also comprehensively examined the association among out-of-pocket costs, TKI initiation (Phase 1) and adherence (Phase 2) with healthcare utilization and costs. Based on literature review, this has not been attempted to study the use of TKIs among CML patients.

Specific Aims

The research goal is to assess the relationship between patient prescription cost sharing, tyrosine kinase inhibitors (TKIs) initiation and adherence, and healthcare utilization and economic outcomes in a large group of commercially insured patients with newly diagnosed chronic myeloid leukemia (CML).

Study One: How Patient Cost Sharing of Tyrosine Kinase Inhibitors Affects Initiation, and Healthcare Utilization in Patients With Newly Diagnosed Chronic Myeloid Leukemia

The specific aim in Journal Article 1 is to examine the association between

patient cost sharing with TKI initiation, and healthcare utilization and costs in commercially insured patients with newly diagnosed CML.

Hypothesis 1 – Increased out-of-pocket costs are associated with patients delaying initiation of TKI therapy.

Hypothesis 2 – Delayed TKI initiation is associated with more emergency room visits and hospitalizations.

Hypothesis 3 – Delayed TKI initiation is associated with higher annual medical costs.

Study Two: Tyrosine Kinase Inhibitors and the Relationship to Adherence, Costs and Healthcare Utilization in Commercially Insured Patients With Newly Diagnosed Chronic Myeloid Leukemia

The specific aim in Journal Article 2 is to examine the association between patient cost sharing with TKI adherence, and also the impact of TKI adherence on subsequent healthcare utilization and costs in commercially insured patients with newly diagnosed CML.

Hypothesis 1 – Increased out-of-pocket costs are associated with patients' non-adherence to TKI therapy.

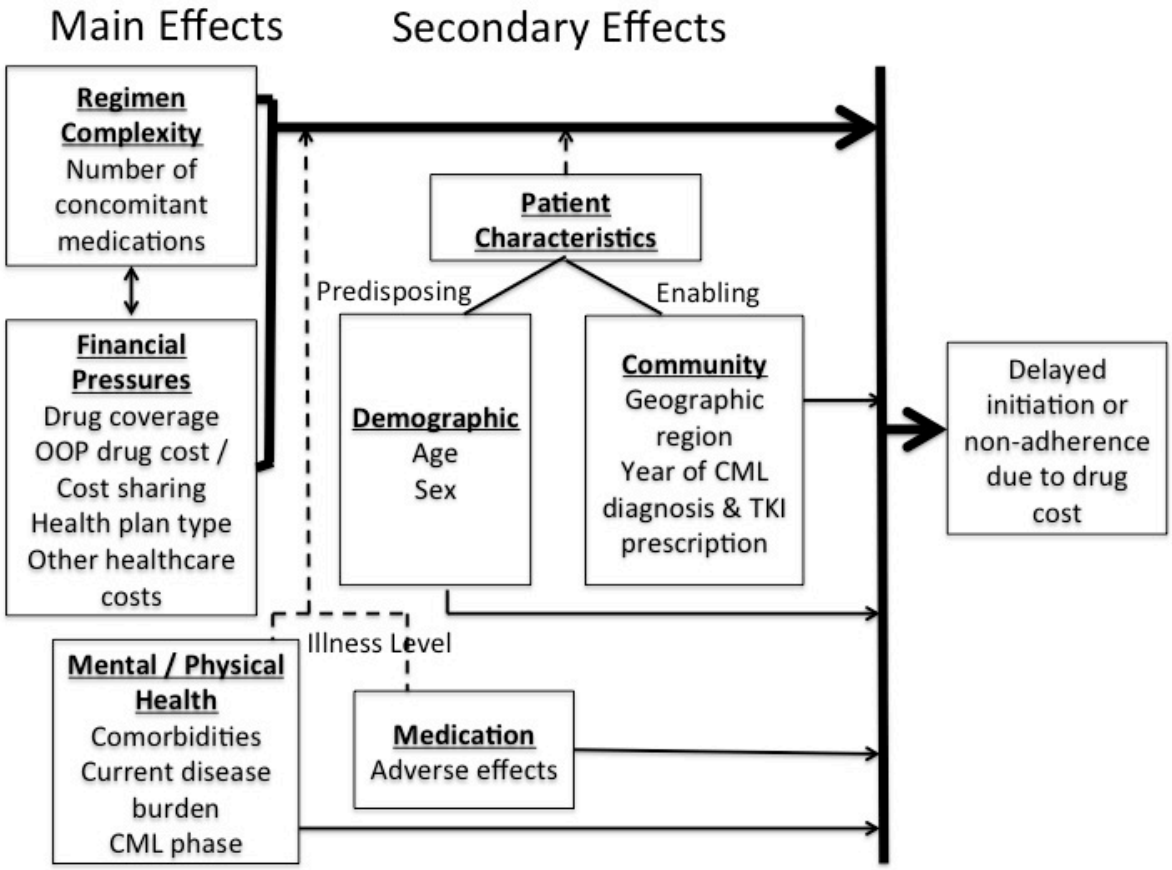
Hypothesis 2 – Higher TKI adherence is associated with fewer emergency room visits and hospitalizations.

Hypothesis 3 – Higher TKI adherence is associated with lower annual medical costs.

Conceptual Framework

To identify predictors of TKI therapy initiation and adherence, this dissertation examined a set of demographic and clinical characteristics selected with the guidance of relevant conceptual models found in the literature. [30,55,56]

Figure 1: Factors Influencing Delayed Initiation or Non-Adherence Due to Drug Cost



Thick black lines represent the ‘‘main effects’’ of financial pressures and regimen complexity on initiation and adherence. Thin dashed lines represent the moderating effects of other domains on patients’ response to cost pressures.
CML indicates chronic myeloid leukemia; OOP, out-of-pocket; TKI, tyrosine kinase inhibitor.

The Andersen & Newman model [55] suggests that use of health services, including prescription medications, is a function of patients' predisposition to use healthcare services, factors that enable or impede patients' ability to use services, and their illness level. Predisposing variables describe the propensity of individuals to seek care, and include demographics such as age and sex. Enabling variables describe the means available to individuals to use services, including geographic region that could affect availability of medical care resources. Briesacher et al. [30] and Piette et al.'s [56] models focus specifically on patients at risk for cost-related medication non-adherence. They conceptualized that a patient's decision to take less medication than prescribed to cut costs can be predicted with risk factors that could be categorized as main or secondary effects. Main effects include financial pressures (e.g., drug cost sharing) and poly-pharmacy (e.g., number of concomitant medications). Secondary effects refer to patients' demographic and clinical characteristics. Predictors of TKI non-adherence have been predominantly studied in patients receiving imatinib [57] since imatinib was the first TKI approved, and has been considered the standard of care for more than a decade [13,14].

Main Effects – Financial Pressures and Regimen Complexity

Variables for financial pressures include enrollment in prescription drug coverage, TKI out-of-pocket costs, health plan type, and other out-of-pocket costs paid by the patient for inpatient and outpatient services, and pharmacy medications (excluding TKI medication). In the conceptual framework, TKI out-of-pocket costs

are hypothesized as the main effect that has a direct association with TKI initiation and adherence.

Regimen complexity variables include the number of unique drug classes filled as a measure of pill burden. Number of concomitant medications is a significant predictor of adherence.[57] Adherence to cancer medications was found to decrease with an increase in the number of medications (cancer and non-cancer) patients were required to take[20,58-60], but one study found a higher concomitant of drug burden related to higher rates of medication adherence[27].

Secondary Effects – Predisposing, Enabling and Illness Level Factors

A series of predisposing, enabling, and illness level factors are hypothesized to explain patients' initiation of and adherence to TKIs. Specifically, predisposing variables include age and sex. There were inconsistent findings as to whether younger or older age was related to better adherence[46,57,61], with studies identifying older age as being associated with non-adherence[20], adherence as being associated with increasing age[58,62], and younger age to be related to non-adherence[21,59]. Sex was also not consistently found to be associated with adherence[46,57,61], with studies reporting females having higher rates of medication non-adherence[48] or lower levels of adherence[58], and males as being related to higher rates of medication non-adherence[20].

Enabling variables include patient's relationship to subscriber, geographic

region, and year of CML diagnosis and TKI prescription. Illness level variables include Deyo-Charlson comorbidity index as a measure of comorbidity burden [63], Darkow CML Complexity Index score as a measure of the difficulty of managing patient's disease [48], the starting dose of the index TKI as a proxy for the phase of CML disease [48,64], and an indicator variable for whether the patient had any dose decrease of the TKI as a proxy for medication adverse effects [10]. Patients who reported higher cancer related complexity [48] had higher rates of medication non-adherence while patients with more cancer related complications also reported lower levels of medication adherence [58]. Imatinib dose is a significant predictor of adherence. [57] Higher dosage or an increase in medication dosage was found to be associated with higher levels of non-adherence. [20,21,48,50,59-61,65] Patients experiencing adverse effects from the medication were more likely to be non-adherent. [21,27,46,57,61,66]

DATA SOURCE

This study utilized 2011-2015 medical and pharmacy claims data collected from the IBM® MarketScan® Commercial Database to provide a representative sample of private health plans in the United States. [67] This database represents active employees and their dependents, early retirees, and Consolidated Omnibus Budget Reconciliation Act (COBRA) continuees insured by large employer-sponsored plans. This insurance claims data set contains information on over 200 million person-years of utilization, cost, and eligibility records, and it has been widely

used for statistical analysis because it encompasses 40 to 50 million privately insured individuals each year, which is more than one quarter of the privately insured US population [68]. The database is considered to be nationally representative of persons with employer-sponsored health insurance with respect to geography, age, and gender. The data include monthly enrollment, inpatient and outpatient medical claims, outpatient prescription drug claims, and reimbursed amounts paid by the health plan and patient for services billed.

Human Subjects Considerations

The dissertation is determined to qualify for exempt status by The University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects (HSC-SPH-17-0752) on August 18, 2017. All data were de-identified in accordance with the Health Insurance Portability and Accountability Act (HIPAA) requirements.

JOURNAL ARTICLE 1

How Patient Cost Sharing of Tyrosine Kinase Inhibitors Affects Initiation, and Healthcare Utilization in Patients With Newly Diagnosed Chronic Myeloid Leukemia: A Retrospective Claims-Based Study

Journal of Managed Care and Specialty Pharmacy

Authorship List: Hsiao Ling Phuar, MSc, BPharm (Hsiao.Ling.Phuar@uth.tmc.edu / 832-788-2801); Charles E. Begley, PhD (Charles.E.Begley@uth.tmc.edu / 713-500-9179); Wenyaw Chan, PhD (Wenyaw.Chan@uth.tmc.edu / 713-500-9321); and Trudy Millard Krause, DrPH, MBA (Trudy.M.Krause@uth.tmc.edu / 713-500-9190)

Author Affiliations: The University of Texas Health Science Center at Houston School of Public Health (HLP, CEB, WC, TMK), Houston, TX.

Source of Funding: Not applicable.

Author Disclosures: All authors report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (HLP); acquisition of data (HLP, TMK); analysis and interpretation of data (HLP); drafting of the manuscript (HLP); critical revision of the manuscript for important intellectual content (HLP, CEB, WC, TMK); statistical analysis (HLP); and supervision (CEB).

Address correspondence to: Hsiao Ling Phuar, MSc, BPharm, PhD Candidate, Department of Management, Policy, and Community Health, The University of Texas Health Science Center at Houston School of Public Health, 1200 Pressler Street, Houston, TX 77030. E-mail: Hsiao.Ling.Phuar@uth.tmc.edu

A poster presentation of the study has been made at the 11th American Association for Cancer Research (AACR) Conference on The Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved on November 2 – 5, 2018.

Abstract

Background: High out-of-pocket costs may lead to disparities in the initiation of and subsequent adherence to expensive medications. For newly diagnosed chronic myeloid leukemia (CML) patients, early access to tyrosine kinase inhibitors (TKIs) is a consistent predictor of adherence and optimal response.

Objective: The study examines the association between TKI out-of-pocket costs, initiation, and response reflected in healthcare utilization and costs among patients who initiated TKI within 12 months following first CML diagnosis.

Methods: Individuals aged 18 to 64 with an initial diagnosis of CML were identified in the IBM® MarketScan® Commercial Database between 4/1/2011 and 12/31/2014. The association between cost-sharing and TKI initiation was evaluated using a multivariate logistic regression model applied to early (patients receiving therapy within a month of diagnosis) and late initiators (1-12 months after diagnosis).

Healthcare utilization was compared using negative binomial regression models. Healthcare cost differences between early and late initiators were estimated using generalized linear models. All models were controlled for potential confounding factors.

Results: The study sample consisted of 477 patients, 397 (83.2%) early initiators and 80 (16.8%) late. Out-of-pocket costs for the initial 30-day supply of TKI medications were not found to be a significant predictor of TKI initiation time. Early initiators were much less likely to have all-cause hospitalizations (IRR=0.35; p=0.02), or CML-specific hospitalizations (IRR=0.27; p<0.01). Over the 12-month follow-up period, early initiators incurred $9,923 more in TKI pharmacy costs (p<0.05), but late initiators incurred $7,582 more in medical costs, $218 more in non-TKI pharmacy costs, and $2,680 in total healthcare costs (p>0.05).

Conclusions: Patients with early TKI initiation had higher TKI pharmacy costs that were more than offset by lower medical and non-TKI pharmacy costs, resulting in lower overall total healthcare costs. Findings suggest that early TKI initiation may reduce the risks of hospitalizations that could result in potential medical cost savings.

Summary Bullets

What is already known about this subject

- Chronic myeloid leukemia (CML) patients are required to take their daily dose of oral tyrosine kinase inhibitors (TKIs) indefinitely for long-term survival.

- Patients initiating anticancer drugs face high out-of-pocket costs because prescription drug plans in the United States tend to have cost-sharing mechanisms in order to control the high costs of these medications.
- Despite the high costs of TKIs, CML patients gain significant health improvements from their optimal use.

What this study adds

- We used commercial insurance claims data to show the association between TKI initiation, and healthcare utilization and costs in patients newly diagnosed with CML.
- Patients with early TKI initiation had lower risk of hospitalizations.
- Patients with early TKI initiation had higher TKI pharmacy costs that were more than offset by lower medical and non-TKI pharmacy costs, resulting in lower overall total healthcare costs.

Introduction

Chronic myeloid leukemia (CML) accounts for 15% of all leukemias in adults.[1] In 2018, an estimated 8,430 people are expected to be diagnosed with CML in the United States, and 1,090 people are expected to die from the disease.[2] CML is usually diagnosed in the chronic phase, but if left untreated, the disease will eventually progress to the advanced phase (accelerated or blast) in less than 5 years.[1,3] The National Comprehensive Cancer Network (NCCN) recommends imatinib, dasatinib, and nilotinib as first-line tyrosine kinase inhibitor (TKI) therapy for

newly diagnosed patients with chronic phase CML. [1] Imatinib was the first TKI approved, and has been considered the standard of care for more than a decade whereas second-generation TKIs, namely dasatinib and nilotinib, are highly effective with the observed improvements in progression-free survival and overall survival in newly diagnosed patients and those who fail imatinib. [4,5] Alternative second- and third-generation TKIs, bosutinib and ponatinib, have also become available as second line options. [1,4,5]

Imatinib and other TKIs have revolutionized the management of CML, making it possible for most CML patients treated with TKIs to experience near normal life expectancy, especially if they were diagnosed before age 65. [6,7] Patients are required to be adherent to their TKI therapy to achieve optimal response and prevent disease progression. [8-10] In addition to adherence, newly diagnosed CML patients who started imatinib within 6 months of diagnosis while in first chronic phase show sustained responses and higher overall survival at a five-year follow-up. [11] Other studies have shown that the cytogenetic and molecular responses, progression-free survival, and event-free survival may be inferior in patients who start imatinib more than 6 months after diagnosis. [12-15] Early prescribing has also been a consistent predictor of adherence. [16] Hence, when indicated, a prescription for TKI therapy should be provided promptly after CML diagnosis as studies found that time since diagnosis for initiation of TKI therapy was associated with the CML patient's level of medication adherence. [16-18] Longer time lag between CML diagnosis and the fill of

the first TKI prescription was associated with higher rates of non-adherence. [8,19] In addition, studies show that non-adherence to treatment may be associated with high annual healthcare costs, since it decreases treatment effectiveness. [20-22]

All these studies underscore the importance of initial access to TKI for patients newly diagnosed with CML who require prompt treatment. [23] Given the expense of these targeted therapies, out-of-pocket costs for initiating therapy may be high and could act as a barrier to starting treatment. In the United States, patients may be subject to out-of-pocket payments of 20% of drug prices that could amount to $20,000 - $30,000 annually. [24] Uninsured patients faced potential prices for chemotherapy that were 2–43 times as much as the total Medicare-allowed amount and 2–5 times as much as the private insurance–allowed amount. [25] Hence, prescription coverage can become quite costly for cancer patients, and having a prescription drug plan does not necessarily mean that it covers all costs for the drugs needed. [26]

In this study, we examined the association between patient cost sharing with TKI initiation, and healthcare utilization and costs. Our study adds to literature in three ways. First, the relationships among out-of-pocket costs, initiation, and healthcare utilization and costs were studied within a single study, which based on literature review is a more comprehensive approach than those that have been used in the past. Second, this study measured actual healthcare utilization and costs in a large group of commercially insured patients with newly diagnosed CML. Third, this

study determined how delays in treatment impact healthcare utilization and overall healthcare costs.

Methods

Data Source

This retrospective claims-based study was conducted using longitudinal inpatient, outpatient, and pharmacy claims data from employer-based, commercially insured group health plans in the United States, covering subscribers and dependents up to age 65. We used the IBM® MarketScan® Commercial Database from January 1, 2011 to December 31, 2015. The MarketScan database captured person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, and prescription drug services. All data were de-identified in accordance with the Health Insurance Portability and Accountability Act (HIPAA) requirements.

Sample Selection

We applied several selection criteria to capture a main sample of patients with newly diagnosed CML. Patients were included if they had at least 1 inpatient or 2 outpatient claims (at least 30 days apart) with a diagnosis of CML between April 1, 2011, and December 31, 2014 (the first of which represents the “index claim”). CML diagnosis is defined using International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code for chronic myeloid leukemia (205.1X), or International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM] code for chronic myeloid leukemia (C92.1X).

Patients were excluded if they were a) younger than age 18 years at index claim date, or turned 65 during the study period, and had b) no continuous enrollment in the health plan in the 3 months before and 12 months after the index claim; c) no drug benefit; d) any claim for a TKI preceding CML diagnosis; e) no claim for a molecular oncogene diagnostic test (during the 30 days before or the 30 days after the index claim); f) not initiate a TKI within 12 months of CML diagnosis; and g) no continuous enrollment in the health plan and drug benefit during the 12 months after TKI initiation.

Study Variables

Measure for TKI out-of-pocket costs. The mean out-of-pocket costs were calculated for the first 30-day supply of TKI medication. Out-of-pocket costs were defined as the sum of the copayments, coinsurance, and deductibles paid by the patient at the time that the first TKI prescription was filled. Out-of-pocket cost amounts for 60- or 90-day prescriptions were adjusted to 30-day amounts. The mean out-of-pocket costs per patient were used, along with other patient characteristics, to predict TKI initiation.

Measure for TKI initiation. The variable measured the time to TKI initiation, defined as the number of months elapsed between the index claim date (first CML diagnosis claim during the study period) and the date that the first TKI prescription was filled during the 12-month post-index period. All TKIs approved for CML and available during the 2011 to 2015 study period (imatinib [Gleevec], dasatinib [Sprycel],

nilotinib [Tasigna], bosutinib [Bosulif], and ponatinib [Iclusig]) were included in the measure definition.

Clinical benefits are most likely to occur when CML patients initiate TKI within 6 months after diagnosis.[11-15] For our study, we used the threshold of one month since patients are expected to begin treatment as soon as they are diagnosed for optimal response.[1] Patients were classified as early initiators of TKI if they had a first claim for a TKI prescription within the first month of CML diagnosis. They were considered to have delayed TKI initiation if their first claim for a TKI prescription occurred after a month of diagnosis and before the end of the 12-month post-index period.

Outcomes

Annual healthcare utilization. We assessed healthcare utilization during the 12-month follow-up period from TKI initiation. Five distinct utilization measures were assessed: (1) number of outpatient physician visits; (2) number of emergency room [ER] visits; (3) number of all-cause hospitalizations; (4) number of CML-specific hospitalizations (identified as any inpatient admission with an ICD-9-CM or ICD-10-CM code for CML as the primary or secondary diagnosis); and (5) number of prescriptions.

Annual healthcare costs. We examined healthcare costs during the 12-month follow-up period from TKI initiation. Costs are reflected in the allowed amount, which

is equal to the sum of plan paid, Coordination of Benefits and Other Savings (COB), and patient out-of-pocket costs, including copayments, coinsurance, and deductibles. Four distinct cost variables were reported: (1) medical costs; (2) TKI pharmacy costs; (3) non-TKI pharmacy costs; and (4) total all-cause healthcare costs – representing aggregated medical and pharmacy costs.

Medical costs included costs associated with any inpatient or outpatient encounter during the 12-month follow-up period. TKI pharmacy costs included costs associated with pharmacy claims for imatinib, dasatinib, nilotinib, bosutinib, and ponatinib during the 12-month follow-up period. Non-TKI pharmacy costs covered costs associated with any other pharmacy claims not included in the TKI pharmacy related cost calculation.

Costs ($US) were converted to 2015 values using the medical component of the Consumer Price Index.

Covariates

Patient characteristics were limited to those variables available in the MarketScan database. We reported demographic characteristics as of the index claim date, such as patient age, sex, year of the index claim, health plan type (comprehensive, preferred provider organization [PPO], point-of-service [POS], consumer-driven health plan/high deductible health plan [CDHP/HDHP], exclusive provider organization [EPO], health maintenance organization [HMO]), region of

residence (Northeast, North Central, South, West), and the patient's relationship to subscriber (subscriber versus spouse or dependent).

We identified clinical characteristics using all available medical and pharmacy claims for study patients in the 3-month pre-index period. These included Deyo-Charlson comorbidity index as a measure of comorbidity burden [27], the number of unique drug classes filled as a measure of pill burden, and Darkow CML Complexity Index score (categorized as usual, moderate, or high, using reported diagnoses of associated complications, comorbidities, or adverse events) as a measure of the difficulty of managing patient's disease [22]. The starting dose of the index TKI medication is used as a proxy for the phase of CML disease. [22,28] This dose was calculated as the strength of TKI dispensed multiplied by the quantity filled, divided by the days' supply on the pharmacy claim. For imatinib, the starting dose was categorized as ≤400mg [i.e., the typical starting dose for chronic phase CML] or ≥600mg [i.e., the typical starting dose for accelerated phase or blast crisis]. [29] For dasatinib, the starting dose was categorized as ≤100mg [i.e., the typical starting dose for chronic phase CML] or ≥140mg [i.e., the typical starting dose for advanced phase]. [30] For nilotinib, the starting dose was categorized as ≤600mg [i.e., the typical starting dose for chronic phase CML] or ≥800mg [i.e., the typical starting dose for accelerated phase]. [31] For bosutinib, the starting dose was categorized as ≤500mg [i.e., the typical starting dose for chronic, accelerated, or blast phase CML in patients resistant to or intolerant to other therapies, including imatinib]. [32] For ponatinib, the

starting dose was categorized as ≤45mg [i.e., the typical starting dose for chronic, accelerated, or blast phase CML in patients for whom no other TKI therapy is indicated]. [33]

An indicator variable for whether the patient was adherent to TKI during the 12-month follow-up was used. We estimated the patient's adherence to TKI using the proportion of days covered (PDC). [34] Patients were classified as adherent to TKIs if they have PDC of at least 80% when they are most likely to achieve clinical benefits from their treatment. [8-10] We used an indicator variable for whether the patient had any TKI dose decrease as a proxy for TKI adverse events during the 12-month follow-up period because TKI toxicities are managed by decreasing the initial dose prescribed. [1] The other control variable was mean other out-of-pocket costs paid by the patient for inpatient and outpatient services, and non-TKI pharmacy medications for the entire 12-month follow-up period.

Statistical Analyses

We conducted statistical comparisons between the characteristics of patients who initiated TKI therapy within 1 month (early initiators) and 1-12 months (late initiators) of CML diagnosis using the Wilcoxon-Mann-Whitney test for continuous variables and Pearson's chi-squared test or the Fisher's exact test (for sparse data with frequency of five or less) for categorical variables.

TKI initiation. We used a multivariate logistic regression model with robust standard

error estimates to calculate the odds of initiating TKI early, controlling for potential confounding factors. We determined the adjusted risk ratio (ARR) and adjusted risk difference (ARD) instead of odds ratio because TKI initiation was considered to be a common event. [35] The ARR is the ratio of the mean predicted probabilities, [36] and represents the probability of TKI initiation for each TKI out-of-pocket cost category after controlling for potential confounding factors. The ARD is the difference of the mean predicted probabilities, [36] and constitutes differences in the absolute risk of initiation.

Healthcare utilization and costs. Healthcare utilization was compared between the early and late initiator cohorts using unadjusted and adjusted incidence rate ratios (IRRs). Adjusted IRRs controlled for potential confounding factors and were estimated using multivariate negative binomial regression models [37]. No offset variable is needed because all outcome variables were observed for a full year.

Unadjusted and adjusted cost differences between the early and late initiator cohorts were estimated using multivariate generalized linear models with a gamma distribution and a log link, [22] controlling for potential confounding factors.

All multivariate regression analyses controlled for the same set of potential confounding factors relevant for the respective study. To study the association between TKI out-of-pocket costs and TKI initiation, the covariates used included patient age, sex, patient's relationship to subscriber, health plan type, region of

residence, CML year of diagnosis, CML phase, type of TKI medication, CML complexity, Deyo-Charlson comorbidity index, and number of concomitant medications. In the estimation of healthcare utilization and costs, the covariates used included an indicator variable of whether the patient is adherent, patient age, sex, patient's relationship to subscriber, health plan type, region of residence, TKI year of initiation, CML phase, type of TKI medication, any TKI dose decrease, CML complexity, Deyo-Charlson comorbidity index, number of concomitant medications, and other out-of-pocket healthcare costs.

All statistical analyses were performed using STATA version 15 (StataCorp LP, College Station, Texas). Statistical significance was assumed at p-values less than 0.05. The study protocol was considered exempt by The University of Texas Health Science Center at Houston Institutional Review Board.

Results

Patient characteristics

There were 477 unique patients newly diagnosed with CML between April 1, 2011 and December 31, 2014, who satisfied the selection criteria for inclusion into our study, where 397 (83.2%) patients were classified as early initiators for initiating TKI within a month from first CML diagnosis, and 80 (16.8%) late initiators for initiating TKI within 1 to 12 months from first CML diagnosis (Figure 2).

Patient characteristics were similar in the early and late TKI initiator cohorts

(Table 1). The mean age was approximately 49 years in the early initiator cohort, and 48 years in the late initiator cohort, although the difference was not statistically significant (p=0.32). Most patients were aged 50-59 years for both early and late initiators. The early initiator cohort contained a significantly (p=0.04) higher percentage of males than the late initiator cohort (56.2% versus 43.8%). The majority of patients in both cohorts were enrolled in the preferred provider organization (PPO) health plan type and lived in the south, which is consistent with the inherent skewness of the MarketScan data set for these groups. Most patients in the early initiator cohort used dasatinib as their index treatment (40.0%), whereas most late initiators used imatinib (43.8%) (p=0.01).

Statistically significant differences (i.e., $p<0.05$) were not observed for CML phase, CML complexity, comorbid conditions, or concomitant medications at baseline. Most patients were in the chronic phase of CML; 94.5% of early initiators and 91.3% of late initiators respectively, and have usual CML complexity; 61.7% and 67.5% respectively. The 10 most prevalent comorbidities found among the study cohorts are reported in Table 1.

The late initiator cohort has slightly higher mean out-of-pocket costs for the first 30-day supply of TKI medication ($231 vs. $190; $p<0.01$). Costs varied substantially among individuals in our sample, with 8.4% of the sample paying more than $400, double the average amount, for the first 30-day supply of TKI. On average, copayments accounted for approximately 81.4% of the initial out-of-pocket

costs for the first 30-day supply of TKI medication, while coinsurance and deductibles accounted for 13.6% and 5.0% respectively. Without taking into account patients who had no TKI out-of-pocket costs, most of the early initiators paid $50 or less (43.3%), whereas a majority of the late initiators incurred more than $100 (33.8%) for their first month supply of TKI medication.

In the unadjusted analysis, TKI initiation was associated with out-of-pocket costs for first TKI supply, patient sex, and index treatment.

TKI initiation

As shown in Table 2, the only factor significantly associated with later treatment initiation was being male (ARR, 0.62; 95% CI, 0.41 to 0.95).

Healthcare utilization and costs

Late initiator patients were observed to have greater healthcare utilization compared to early initiator patients, particularly utilization related to outpatient physician visits, emergency room visits, and hospitalizations (Table 3). On an unadjusted basis, early initiator patients were less likely to have all-cause hospitalizations (IRR=0.29, $p<0.01$); and CML-specific hospitalizations (IRR=0.19, $p<0.01$). After adjusting for potential confounding factors, early initiators were much less likely to have all-cause hospitalizations (IRR=0.35; $p=0.02$), or CML-specific hospitalizations (IRR=0.27; $p<0.01$). Outpatient visits were the most frequently used health service in both study cohorts (early initiators = 17.5 visits, late initiators = 17.8

visits), but unadjusted and adjusted utilization did not vary between these patients ($p>0.05$).

The only significant difference found among the cost components of the total annual all-cause healthcare costs between the two study cohorts was for TKI pharmacy costs (Table 4). We found that early initiators incurred higher TKI pharmacy costs by $9,923 ($p<0.05$). Late initiators, on the other hand, incurred $7,582 more in medical costs, $218 more in non-TKI pharmacy costs, and $2,680 more in total all-cause healthcare costs (all $p>0.05$).

Discussion

Most patients newly diagnosed with CML initiated TKI treatment within a month of diagnosis with no significant association with out-of-pocket costs for the first 30-day supply of TKI medication. This finding is in contrast with other retrospective cohort studies that have found the association between high cost sharing with reduced and/or delayed initiation of TKIs.[23,38-40] These studies, however, compared the effect of cost sharing for Medicare patients between those who faced nominal cost sharing of ≤$5 throughout the year if they quality for full low-income (LIS) subsidies, and fee-for-service non-LIS patients.

To the best of our knowledge, this is the first study to research the association between patient cost sharing and TKI initiation in a population of commercially insured patients newly diagnosed with CML. In our study cohort, 14.5% had no out-

of-pocket costs for their first month supply of TKI, and the majority of patients (41.3%) incurred costs of $50 or less. Out-of-pocket costs for the first 30-day supply of TKI medication averaged $198; median out-of-pocket costs were $42 (range, $0 to $9,443). Costs differed substantially among individuals in our sample, with 8.4% paying twice the estimated average costs for the first 30-day supply of TKI medications.

Available funding resources for commercially insured patients may have helped in enabling them to get initiated on TKIs early after diagnosis of CML. Cancer patients can explore resources such as the Leukemia & Lymphoma Society (LLS) Co-pay Assistance Program; patient assistance or prescription assistance programs, sponsored by major pharmaceutical manufacturers; or prescription savings programs to help finance treatment. [26] However, when these programs are used, the costs are not reflected in the claims data at all.

Further research would be required to determine if there is any association between the continuous monthly out-of-pocket costs that patients incur for TKI medications and their adherence. This is especially pertinent as patient assistance programs are subject to availability of funds as well as the program maximum that is imposed. For example, the LLS Co-pay Assistance Program for CML provides $2,000. [41] The Universal Co-pay Card offered by Novartis Pharmaceuticals Corporation for Gleevec and Tasigna requires that the patient be responsible for up to the first $25 with the remaining co-pay or coinsurance paid for by the program

until the yearly maximum of $15,000 after which the patient is responsible for the difference. [42]

Patients who initiated TKI early have correspondingly higher TKI pharmacy costs. TKIs usually account for the majority of total pharmacy costs. [43] Our findings on total all-cause healthcare costs are consistent with reports using similar claims-based methodology among insured patients. [28] CML is a chronic disease requiring routine follow-up. As expected, outpatient visits were the most used health care, and inpatient and emergency room visits were low in both patient cohorts. These healthcare utilization patterns were consistent with other reports in the literature. [21,22,28] The main finding is that patients who delayed initiation of TKI experienced higher levels of healthcare utilization. Most notably, they were much more likely to have more frequent adjusted all-cause hospitalizations, and adjusted CML-specific hospitalizations (all $p<0.05$).

Our findings have important implications. Oral anticancer medications are typically covered under a pharmacy benefit with substantial out-of-pocket costs due at the time the medication is obtained at the pharmacy. [39] High out-of-pocket costs for TKI medications are significantly associated with delayed access and non-adherence. [38,39,44] Clinical guidelines recommend initiating a TKI immediately after a diagnosis of CML, and patients using these therapies are expected to take them for a long period of time. [45] Low adherence to TKI therapy can decrease response to treatment, which can result in patients requiring stem-cell transplantation, worse

clinical outcomes, and potentially shorter life expectancy.[46] Total healthcare costs are higher for episodes of TKI treatment failures than those of ongoing treatment with the costs increasing with each sequential line of TKI treatment failure.[47,48]

This underscores the importance of having doctors or social workers talk with newly diagnosed CML patients about how to finance treatment and explore resources to help with their expenses. Patients should be made aware that financial support is not only available for low-income individuals. For instance, to be eligible for the LLS Co-pay Assistance Program, one has to be at or below 500% of the U.S. federal poverty guidelines as adjusted by the Cost of Living Index.[41] A single person is eligible if they have a household income at or below $60,700, whereas a household with 4 people is eligible with an income at or below $125,500.[41]

In addition, doctors and pharmacists should focus on assessing the "treatment value" of different TKI therapies in relation to benefits versus cost; for instance, prescribing lower dose dasatinib, which has at least equivalent efficacy compared to second generation TKIs but at a significant lower cost comparable to generic imatinib.[45] Efforts to lower drug prices and subsequently, the out-of-pocket costs for TKI medications could significantly improve adherence, and overall health and economic outcomes among CML patients. Future research should focus on assessing barriers to timely access to healthcare for early diagnosis of CML and optimal TKI adherence to advance the understanding of and eliminate health disparities in cancer.

Limitations

Several study limitations should be noted. Additional clinical and socioeconomic variables that were not available in our claims data raised the potential for unobserved confounding. We sought to minimize the limitations of administrative claims data by employing multivariate regressions to control for a variety of sociodemographic and clinical characteristics that could influence treatment decisions. Other common limitations such as missing data and errors in claims coding may also apply in this study. Nonetheless, claims data provide a valid, big sample source of actual practice data. [43]

The use of insurance claims data included information on filled prescriptions only, and thus, we are unable to determine whether our large group of non-initiators did not receive a prescription, or whether they received a prescription but did not fill it. It is also possible that some patients who were classified as not initiating treatment, or as delaying initiation, may have been receiving medication via other means that would not have resulted in a prescription claim. In some cases, patients may also have supplemental cost-sharing help from patient assistance programs, which would result in our results underestimating the true adverse impact of high cost sharing.

This analysis also only examined patients under age 65. All patients in the study were commercially insured in a plan that offered prescription coverage and are likely healthier and younger than the general population of CML patients. However,

our findings may well be applicable to CML patients aged 65 years and older despite excluding Medicare beneficiaries, who constitute about half of all patients with CML at diagnosis. [21]

The 5-year study period of 2011-2015 allows for a good observation of CML patients receiving imatinib, dasatinib, and nilotinib, which were the first three TKIs approved by the US Food and Drug Administration (FDA) for CML treatment in 2001, 2006, and 2007 respectively. [49] This resulted in our study having a negligible number of CML patients on bosutinib and ponatinib, two TKIs that were approved by the FDA for CML treatment in 2012. [49]

Conclusions

Our study suggests that patients with early TKI initiation were at lower risk of adverse events such as hospitalizations, resulting in lower medical costs. These would offset their higher TKI pharmacy costs leading to lower overall total healthcare costs.

References

1. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Chronic myeloid leukemia. https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. Updated 2018. Accessed June 23, 2018.

2. National Cancer Institute SEER Program. Cancer stat facts: Leukemia - chronic myeloid leukemia (CML). https://seer.cancer.gov/statfacts/html/cmyl.html. Updated 2018. Accessed August 4, 2018.

3. Sawyers CL. Chronic myeloid leukemia. *N Engl J Med*. 1999;340(17):1330-1340. https://www-nejm-org.utsph.idm.oclc.org/doi/full/10.1056/NEJM199904293401706. Accessed June 23, 2018.

4. Mathisen MS, Kantarjian HM, Cortes J, Jabbour EJ. Practical issues surrounding the explosion of tyrosine kinase inhibitors for the management of chronic myeloid leukemia. *Blood Rev*. 2014;28(5):179-187. https://www.bloodreviews.com/article/S0268-960X(14)00042-3/fulltext. Accessed June 23, 2018.

5. Cuellar S, Vozniak M, Rhodes J, Forcello N, Olszta D. BCR-ABL1 tyrosine kinase inhibitors for the treatment of chronic myeloid leukemia. *J Oncol Pharm Pract*. 2017.

http://journals.sagepub.com.utsph.idm.oclc.org/doi/abs/10.1177/1078155217710553. Accessed June 23, 2018.

6. National Cancer Institute. Chronic myelogenous leukemia treatment - health professional version. https://www.cancer.gov/types/leukemia/hp/cml-treatment-pdq. Updated 2018. Accessed June 23, 2018.

7. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67:7-30. https://onlinelibrary.wiley.com/doi/10.3322/caac.21387. Accessed June 23, 2018.

8. Noens L, van Lierde MA, De Bock R, et al. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: The ADAGIO study. *Blood*. 2009;113(22):5401-5411. http://www.bloodjournal.org/content/113/22/5401.short?sso-checked=true. Accessed June 23, 2018.

9. Marin D, Bazeos A, Mahon F, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *J Clin Oncol*. 2010;28(14):2381-2388. http://ascopubs.org/doi/full/10.1200/JCO.2009.26.3087. Accessed June 23, 2018.

10. Ibrahim AR, Eliasson L, Apperley JF, et al. Poor adherence is the main reason for loss of CCyR and imatinib failure for chronic myeloid leukemia patients on long-

term therapy. *Blood*. 2011;117(14):3733-3736. http://www.bloodjournal.org/content/117/14/3733. Accessed June 23, 2018.

11. Druker BJ, Guilhot F, O'brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med*. 2006;355(23):2408-2417. https://www-nejm-org.utsph.idm.oclc.org/doi/full/10.1056/NEJMoa062867. Accessed June 23, 2018.

12. Jiang H, Chen S, Jiang B, et al. Seven-year response to imatinib as initial treatment versus re-treatment in chinese patients with chronic myelogenous leukemia in the chronic phase. *Ann Hematol*. 2011;90(1):41-46. https://doi-org.utsph.idm.oclc.org/10.1007/s00277-010-1031-0. Accessed June 23, 2018.

13. Kurtovic-Kozaric A, Hasic A, Radich JP, et al. The reality of cancer treatment in a developing country: The effects of delayed TKI treatment on survival, cytogenetic and molecular responses in chronic myeloid leukaemia patients. *Br J Haematol*. 2016;172(3):420-427. https://onlinelibrary-wiley-com.utsph.idm.oclc.org/doi/full/10.1111/bjh.13843. Accessed June 23, 2018.

14. Beinortas T, Tavorienė I, Žvirblis T, Gerbutavičius R, Jurgutis M, Griškevičius L. Chronic myeloid leukemia incidence, survival and accessibility of tyrosine kinase inhibitors: A report from population-based lithuanian haematological disease registry 2000–2013. *BMC Cancer*. 2016;16:198. https://bmccancer-biomedcentral-

com.utsph.idm.oclc.org/articles/10.1186/s12885-016-2238-9. Accessed June 23, 2018.

15. Palandri F, Iacobucci I, Martinelli G, et al. Long-term outcome of complete cytogenetic responders after imatinib 400 mg in late chronic phase, philadelphia-positive chronic myeloid leukemia: The GIMEMA working party on CML. *J Clin Oncol*. 2008;26(1):106-111. http://ascopubs.org/doi/abs/10.1200/JCO.2007.13.2373. Accessed June 23, 2018.

16. Jabbour E, Saglio G, Radich J, Kantarjian H. Adherence to BCR-ABL inhibitors: Issues for CML therapy. *Clin Lymphoma Myeloma Leuk*. 2012;12(4):223-229. https://www.clinical-lymphoma-myeloma-leukemia.com/article/S2152-2650(12)00056-0/fulltext. Accessed June 23, 2018.

17. Hall AE, Paul C, Bryant J, et al. To adhere or not to adhere: Rates and reasons of medication adherence in hematological cancer patients. *Crit Rev Oncol*. 2016;97:247-262. https://www.croh-online.com/article/S1040-8428(15)30040-8/fulltext. Accessed June 23, 2018.

18. Henk HJ, Woloj M, Shapiro M, Whiteley J. Real-world analysis of tyrosine kinase inhibitor treatment patterns among patients with chronic myeloid leukemia in the united states. *Clin Ther*. 2015;37(1):124-133. https://www.clinicaltherapeutics.com/article/S0149-2918(14)00692-4/fulltext. Accessed June 23, 2018.

19. StCharles M, Bollu VK, Hornyak E, Coombs J, Blanchette CM, DeAngelo DJ. Predictors of treatment non-adherence in patients treated with imatinib mesylate for chronic myeloid leukemia. *Blood*. 2009;114(22):2209. http://www.bloodjournal.org/content/114/22/2209. Accessed June 23, 2018.

20. Alves AR, Lima WG, Nagai MM, Rodrigues JPV, Ayres LR. Adherence and/or discontinuation of imatinib mesylate in patients with chronic myeloid leukemia. *Braz J Pharm Sci*. 2016;52(4):581-589. http://www.scielo.br.utsph.idm.oclc.org/scielo.php?pid=S1984-82502016000400581&script=sci_arttext. Accessed June 23, 2018.

21. Wu EQ, Johnson S, Beaulieu N, et al. Healthcare resource utilization and costs associated with non-adherence to imatinib treatment in chronic myeloid leukemia patients. *Curr Med Res Opin*. 2010;26(1):61-69. https://www-tandfonline-com.utsph.idm.oclc.org/doi/abs/10.1185/03007990903396469. Accessed June 23, 2018.

22. Darkow T, Henk HJ, Thomas SK, et al. Treatment interruptions and non-adherence with imatinib and associated healthcare costs. *Pharmacoeconomics*. 2007;25(6):481-496. https://link-springer-com.utsph.idm.oclc.org/article/10.2165/00019053-200725060-00004. Accessed June 23, 2018.

23. Doshi JA, Li P, Huo H, et al. High cost sharing and specialty drug initiation under medicare part D: A case study in patients with newly diagnosed chronic myeloid leukemia. *Am J Manag Care*. 2016;22(4 Suppl):S78-S86. https://www.ajmc.com/journals/supplement/2016/improving-patient-access-to-critical-therapies-in-the-age-of-cost-sharing/high-cost-sharing-and-specialty-drug-initiation-under-medicare-part-d-a-case-study-in-patients-with-newly-diagnosed-cml. Accessed June 23, 2018.

24. Experts in Chronic Myeloid Leukemia. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: From the perspective of a large group of CML experts. *Blood*. 2013;121(22):4439-4442. http://www.bloodjournal.org/content/121/22/4439.full. Accessed June 23, 2018.

25. Dusetzina SB, Basch E, Keating NL. For uninsured cancer patients, outpatient charges can be costly, putting treatments out of reach. *Health Aff*. 2015;34(4):584-591. https://www-healthaffairs-org.utsph.idm.oclc.org/doi/full/10.1377/hlthaff.2014.0801. Accessed June 26, 2018.

26. Leukemia & Lymphoma Society. Financial support. https://www.lls.org/support/financial-support. Updated 2018. Accessed November 7, 2018.

27. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619.

https://www-sciencedirect-com.utsph.idm.oclc.org/science/article/pii/0895435692901338. Accessed June 23, 2018.

28. Ward MA, Fang G, Richards KL, et al. Comparative evaluation of patients newly initiating first-generation versus second-generation tyrosine kinase inhibitors for chronic myeloid leukemia and medication adherence, health services utilization, and healthcare costs. *Curr Med Res Opin*. 2015;31(2):289-297. https://www-tandfonline-com.utsph.idm.oclc.org/doi/abs/10.1185/03007995.2014.991440. Accessed June 25, 2018.

29. Medscape. Imatinib (rx). http://reference.medscape.com/drug/gleevec-imatinib-342239. Updated 2018. Accessed June 23, 2018.

30. Medscape. Dasatinib (rx). http://reference.medscape.com/drug/sprycel-dasatinib-342199. Updated 2018. Accessed June 23, 2018.

31. Medscape. Nilotinib (rx). http://reference.medscape.com/drug/tasigna-nilotinib-342198. Updated 2018. Accessed June 23, 2018.

32. Medscape. Bosutinib (rx). http://reference.medscape.com/drug/bosulif-bosutinib-999770. Updated 2018. Accessed June 23, 2018.

33. Medscape. Ponatinib (rx). http://reference.medscape.com/drug/iclusig-ponatinib-999800. Updated 2018. Accessed June 23, 2018.

34. Nau DP. Proportion of days covered (PDC) as a preferred method of measuring medication adherence. *Springfield, VA: Pharmacy Quality Alliance*. 2012. http://ep.yimg.com/ty/cdn/epill/pdcmpr.pdf. Accessed June 23, 2018.

35. Kleinman LC, Norton EC. What's the risk? A simple approach for estimating adjusted risk measures from nonlinear models including logistic regression. *Health Serv Res*. 2009;44(1):288-302. https://www-ncbi-nlm-nih-gov.utsph.idm.oclc.org/pmc/articles/PMC2669627/. Accessed July 5, 2018.

36. Norton EC, Miller MM, Kleinman LC. Computing adjusted risk ratios and risk differences in stata. *Stata J*. 2013;13(3):492-509. https://pdfs.semanticscholar.org/28cb/e7852bb3d11c5e9518c0a7a06ce022a89ccb.pdf. Accessed July 5, 2018.

37. UCLA Institute for Digital Research and Education. Regression models with count data. https://stats.idre.ucla.edu/stata/seminars/regression-models-with-count-data/. Updated 2018. Accessed July 6, 2018.

38. Winn AN, Keating NL, Dusetzina SB. Factors associated with tyrosine kinase inhibitor initiation and adherence among medicare beneficiaries with chronic myeloid leukemia. *J Clin Oncol*. 2016;34(36):4323-4328. https://www-ncbi-nlm-nih-gov.utsph.idm.oclc.org/pmc/articles/PMC5455309/. Accessed June 25, 2018.

39. Doshi JA, Li P, Huo H, Pettit AR, Armstrong KA. Association of patient out-of-pocket costs with prescription abandonment and delay in fills of novel oral anticancer agents. *J Clin Oncol*. 2018;36(5):476-482. http://ascopubs.org/doi/10.1200/JCO.2017.74.5091. Accessed June 25, 2018.

40. Shen C, Zhao B, Liu L, Shih YT. Financial burden for patients with chronic myeloid leukemia enrolled in medicare part D taking targeted oral anticancer medications. *J Oncol Pract*. 2017;13(2):e152-e162. http://ascopubs.org/doi/abs/10.1200/JOP.2016.014639. Accessed June 25, 2018.

41. Leukemia & Lymphoma Society. Co-pay assistance program. https://www.lls.org/support/financial-support/co-pay-assistance-program. Updated 2018. Accessed November 7, 2018.

42. RxAssist. Provider center. https://www.rxassist.org/providers. Updated 2018. Accessed November 7, 2018.

43. Wu EQ, Guerin A, Yu AP, Bollu VK, Guo A, Griffin JD. Retrospective real-world comparison of medical visits, costs, and adherence between nilotinib and dasatinib in chronic myeloid leukemia. *Curr Med Res Opin*. 2010;26(12):2861-2869. https://www-tandfonline-com.utsph.idm.oclc.org/doi/abs/10.1185/03007995.2010.533648. Accessed June 25, 2018.

44. Dusetzina SB, Winn AN, Abel GA, Huskamp HA, Keating NL. Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. *J Clin Oncol*. 2013;32(4):306-311. http://ascopubs.org/doi/full/10.1200/JCO.2013.52.9123. Accessed June 26, 2018.

45. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2018 update on diagnosis, therapy and monitoring. *Am J Hematol*. 2018;93(3):442-459. https://onlinelibrary-wiley-com.utsph.idm.oclc.org/doi/full/10.1002/ajh.25011. Accessed June 26, 2018.

46. Jabbour EJ, Kantarjian H, Eliasson L, Megan Cornelison A, Marin D. Patient adherence to tyrosine kinase inhibitor therapy in chronic myeloid leukemia. *Am J Hematol*. 2012;87(7):687-691. https://onlinelibrary-wiley-com.utsph.idm.oclc.org/doi/full/10.1002/ajh.23180. Accessed June 26, 2018.

47. Knopf KB, Divino V, McGarry L, et al. Economic burden of tyrosine kinase inhibitor treatment failure in chronic myeloid leukemia. *Clin Lymphoma Myeloma Leuk*. 2015;15(11):e163-e171. https://www.clinical-lymphoma-myeloma-leukemia.com/article/S2152-2650(15)01079-4/fulltext. Accessed June 25, 2018.

48. McGarry LJ, Chen YJ, Divino V, et al. Increasing economic burden of tyrosine kinase inhibitor treatment failure by line of therapy in chronic myeloid leukemia. *Curr Med Res Opin*. 2016;32(2):289-299. https://www-tandfonline-com.utsph.idm.oclc.org/doi/abs/10.1185/03007995.2015.1120189. Accessed June 25, 2018.

49. CenterWatch. FDA approved drugs for oncology. http://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/12/oncology. Updated 2018. Accessed June 26, 2018.

Table 1: Sample Characteristics by TKI Initiation Time from First CML Diagnosis

	Patients who initiated TKI therapy		p-value[a]
	In 1 month or less from first CML diagnosis (n = 397)	Within 1-12 months from first CML diagnosis (n = 80)	
Demographic characteristics			
Age at the index date, years, mean±SD [median]	49.10±10.49 [51]	47.59±11.35 [49.5]	0.32
Age group, years, n			0.35
18 – 39	71 (17.9%)	21 (26.3%)	
40 – 49	101 (25.4%)	19 (23.8%)	
50 – 59	166 (41.8%)	28 (35.0%)	
60 – 64	59 (14.9%)	12 (15.0%)	
Male, n	223 (56.2%)	35 (43.8%)	0.04[b]
Patient's relationship to subscriber, n			0.80
Subscriber	264 (66.5%)	52 (65.0%)	
Spouse or dependent	133 (33.5%)	28 (35.0%)	
Health plan type, n			0.64
Group: Comprehensive / Preferred provider organization / Point-of-service / Exclusive provider organization	292 (73.6%)	56 (70.0%)	
Consumer-driven health plan / high deductible health plan	40 (10.1%)	11 (13.8%)	
Health maintenance organization	37 (9.3%)	9 (11.3%)	

	Patients who initiated TKI therapy		p-value[a]
	In 1 month or less from first CML diagnosis (n = 397)	Within 1-12 months from first CML diagnosis (n = 80)	
Missing / Unknown	28 (7.1%)	4 (5.0%)	
Region of residence, n			0.29
Northeast	88 (22.2%)	11 (13.8%)	
North Central	83 (20.9%)	14 (17.5%)	
South	152 (38.3%)	40 (50.0%)	
West	64 (16.1%)	13 (16.3%)	
Unknown	10 (2.5%)	2 (2.5%)	
Index year, n			0.29
2011	101 (25.4%)	26 (32.5%)	
2012	111 (28.0%)	26 (32.5%)	
2013	95 (23.9%)	14 (17.5%)	
2014	90 (22.7%)	14 (17.5%)	
Time to drug index date from diagnosis date, days, mean±SD [median]	12.05±7.75 [11]	85.68 ±63.08 [68.5]	<0.001[b]
Index treatment, n			0.01[b]
Imatinib			
Started on ≤400 mg/day	138 (34.8%)	35 (43.8%)	
Started on ≥600 mg/day	9 (2.3%)	0	
Dasatinib			
Started on ≤100 mg/day	157 (39.5%)	21 (26.3%)	

	Patients who initiated TKI therapy		p-value[a]
	In 1 month or less from first CML diagnosis (n = 397)	Within 1-12 months from first CML diagnosis (n = 80)	
Started on ≥140 mg/day	2 (0.5%)	0	
Nilotinib			
Started on ≤600 mg/day	80 (20.2%)	17 (21.3%)	
Started on ≥800 mg/day	11 (2.8%)	5 (6.3%)	
Bosutinib			
Started on ≤500mg/day	0	1 (1.2%)	
Ponatinib			
Started on ≤45mg/day	0	1 (1.2%)	
CML chronic phase, n	375 (94.5%)	73 (91.3%)	0.27
Darkow CML Complexity Index, n			0.55
Usual	245 (61.7%)	54 (67.5%)	
Moderate	96 (24.2%)	15 (18.8%)	
High	56 (14.1%)	11 (13.8%)	
Deyo-Charlson comorbidity index, mean±SD [median]	2.38±0.96 [2]	2.59±1.47 [2]	0.75
10 most prevalent comorbidities, n			-[c]
Diabetes	42 (10.6%)	8 (10.0%)	
Chronic obstructive pulmonary	23 (5.8%)	4 (5.0%)	
Cerebrovascular	6 (1.5%)	1 (1.3%)	
Rheumatoid disease	6 (1.5%)	1 (1.3%)	

	Patients who initiated TKI therapy		p-value[a]
	In 1 month or less from first CML diagnosis (n = 397)	Within 1-12 months from first CML diagnosis (n = 80)	
Acute myocardial	6 (1.5%)	0	
Metastatic cancer	5 (1.3%)	4 (5.0%)	
Renal	5 (1.3%)	1 (1.3%)	
Congestive heart	4 (1.0%)	2 (2.5%)	
Peripheral vascular	4 (1.0%)	1 (1.3%)	
Hemiplegia / paraplegia	2 (0.5%)	0	
Concomitant medications / Number of unique drug classes, mean±SD [median]	3.79±3.19 [3]	3.41±3.31 [3]	0.19
Out-of-pocket costs for first 30 days' supply of TKI medication, $, mean±SD [median]	189.37±683.14 [36.79]	230.24±645.48 [56.06]	<0.01[b]
Out-of-pocket costs group, n			0.04[b]
$0	60 (15.1%)	9 (11.2%)	
>$0 – $50	172 (43.3%)	25 (31.2%)	
>$50 – $100	84 (21.2%)	19 (23.8%)	
>$100	81 (20.4%)	27 (33.8%)	

[a] Comparing the differences between patients who initiated TKI therapy ≤ 1 month and 1-12 months. Continuous variables were compared using the Wilcoxon-Mann-Whitney test. Categorical variables were compared using Pearson's chi-squared test or the Fisher's exact test if one or more cells have an expected frequency of five or less.
[b] Significant at the 5% level.
[c] P-values not presented because data is too sparse.
CML indicates chronic myeloid leukemia; TKI, tyrosine kinase inhibitor.

Table 2: Adjusted Risk Ratio (ARR) and Adjusted Risk Difference (ARD) of TKI Initiation Among Individuals With CML (n=477)

Characteristics	ARR[a]	95% CI	ARD[a]	95% CI
Mean out-of-pocket costs for first 30-day supply of TKI medication				
$0	Reference		Reference	
>$0 – $50	1.06	0.53 to 2.11	0.01	-0.11 to 0.13
>$50 – $100	1.30	0.65 to 2.60	0.05	-0.09 to 0.18
>$100	1.64	0.86 to 3.12	0.09	-0.04 to 0.22
Age at the index date, years				
18 – 39	Reference		Reference	
40 – 49	0.73	0.39 to 1.37	-0.05	-0.14 to 0.04
50 – 59	0.69	0.40 to 1.18	-0.06	-0.14 to 0.02
60 – 64	0.84	0.42 to 1.67	-0.03	-0.13 to 0.07
Male versus female[b]	0.62	0.41 to 0.95	-0.08	-0.15 to -0.01
Subscriber (yes versus no)	1.03	0.66 to 1.60	0.00	-0.07 to 0.08
Health plan type				
Group: Comprehensive / Preferred provider organization / Point-of-service / Exclusive provider organization	Reference		Reference	
Consumer-driven health plan / high deductible health plan	1.46	0.80 to 2.67	0.07	-0.06 to 0.20
Health maintenance organization	1.19	0.61 to 2.33	0.03	-0.10 to 0.16
Missing / Unknown	0.98	0.39 to 2.49	-0.00	-0.15 to 0.15

Characteristics	ARR[a]	95% CI	ARD[a]	95% CI
Region of residence				
South	Reference		Reference	
Northeast	0.57	0.28 to 1.13	-0.08	-0.16 to 0.00
North Central	0.71	0.40 to 1.25	-0.05	-0.13 to 0.03
West	0.87	0.50 to 1.53	-0.02	-0.11 to 0.06
Unknown	0.86	0.21 to 3.46	-0.03	-0.22 to 0.18
Index year				
2011	Reference		Reference	
2012	0.88	0.53 to 1.47	-0.02	-0.10 to 0.06
2013	0.60	0.32 to 1.13	-0.07	-0.15 to 0.00
2014	0.68	0.37 to 1.24	-0.06	-0.14 to 0.02
Index treatment				
Imatinib	Reference		Reference	
Dasatinib	0.66	0.40 to 1.10	-0.06	-0.14 to 0.01
Nilotinib	1.16	0.71 to 1.90	0.03	-0.06 to 0.11
Chronic phase CML (yes versus no)	0.82	0.36 to 1.87	-0.04	-0.20 to 0.13
Darkow CML Complexity Index				
Usual	Reference		Reference	
Moderate	0.76	0.45 to 1.26	-0.04	-0.11 to 0.03
High	1.00	0.56 to 1.78	0.00	-0.09 to 0.10
Deyo-Charlson comorbidity index[c]	1.24	1.00 to 1.54	0.02	0.01 to 0.04
Concomitant medications / Number of unique drug	0.98	0.91 to 1.04	-0.00	-0.02 to 0.01

Characteristics	ARR[a]	95% CI	ARD[a]	95% CI
classes[c]				

[a] ARR and ARD were determined using a multivariate logistic regression model with robust standard error estimates.
[b] Significant at the 5% level.
[c] Treated as continuous.
ARD indicates adjusted risk difference; ARR, adjusted risk ratio; CI, confidence interval; CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor.

Table 3: Comparison of Healthcare Utilization Between Early and Late TKI Initiator Patients

	Average Annual Utilization (mean±SD)		Unadjusted		Adjusted	
	Patients who initiated TKI therapy					
	In 1 month or less from first CML diagnosis (n = 397)	Within 1-12 months from first CML diagnosis (n = 80)	IRR[a]	p-value	IRR[a]	p-value
Outpatient physician visits	17.49±9.81	17.80±14.89	0.98	0.86	1.01	0.89
Emergency room (ER) visits	0.54±1.98	0.79±2.11	0.69	0.29	0.73	0.27
All-cause hospitalizations	0.08±0.45	0.26±0.82	0.29	<0.01[b]	0.35	0.02[b]
CML-specific hospitalizations	0.04±0.24	0.21±0.77	0.19	<0.01[b]	0.27	<0.01[b]
Number of prescriptions (all drugs)	34.35±27.22	37.60±31.81	0.91	0.38	0.88	0.09
Number of TKI prescriptions	10.23±3.41	9.79±4.48	1.05	0.41	0.99	0.77
Number of non-TKI prescriptions	24.12±26.54	27.81±30.60	0.87	0.29	0.81	0.06

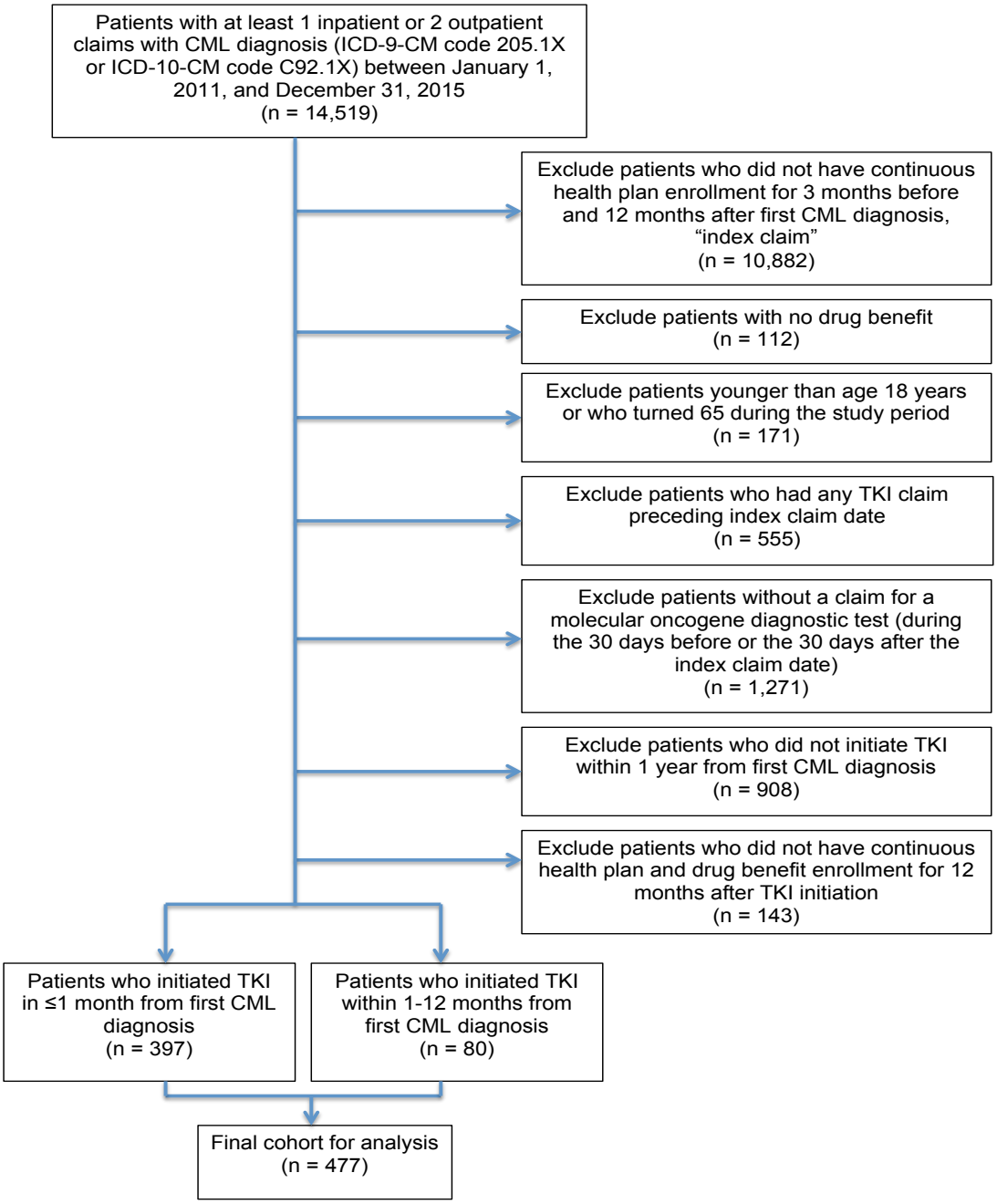
[a] An IRR >1 indicates that early initiator patients had higher incidence of incurring medical services compared to late initiator patients. IRR were estimated using multivariate negative binomial regressions.
[b] Significant at the 5% level.
CML indicates chronic myeloid leukemia; IRR, incidence rate ratio; TKI, tyrosine kinase inhibitor.

Table 4: Comparison of Healthcare Costs Between Early and Late TKI Initiator Patients

	Average Annual Costs,$ (mean±SD)		Unadjusted		Adjusted	
	Patients who initiated TKI therapy					
	In 1 month or less from first CML diagnosis (n = 397) [A]	Within 1-12 months from first CML diagnosis (n = 80) [B]	Cost Difference[a] [A] – [B]	p-value	Cost Difference[a] (beta coefficient)	p-value
Medical costs	18,022.82±47,196.26	37,385.61±102,911.10	-19,362.79	0.03[b]	-7,581.78 (-.29)	0.22
TKI pharmacy costs	100,261.80±32,276.67	85,516.64±37,864.63	14,745.16	<0.01[b]	9,922.02 (.11)	<0.05[b]
Non-TKI pharmacy costs	2,580.74±6,031.22	2,644.48±4,655.23	-63.74	0.92	-217.17 (-.05)	0.80
Total all-cause healthcare costs	120,865.40± 57,195.23	125,546.70±108,251.90	-4,681.30	0.70	-2,679.20 (-.02)	0.79

[a] Cost differences <0 indicate that late initiators incurred higher healthcare costs. Cost differences were estimated using multivariate generalized linear models with a gamma distribution and a log link.
[b] Significant at the 5% level.
TKI indicates tyrosine kinase inhibitor.

Figure 2: Study Cohort Selection and Subject Exclusion



JOURNAL ARTICLE 2

Tyrosine Kinase Inhibitors and the Relationship to Adherence, Costs and Healthcare Utilization in Commercially Insured Patients With Newly Diagnosed Chronic Myeloid Leukemia: A Retrospective Claims-Based Study

Current Medical Research and Opinion

Authorship List: Hsiao Ling Phuar, MSc, BPharm; Charles E. Begley, PhD; Wenyaw Chan, PhD; and Trudy Millard Krause, DrPH, MBA

Author Affiliations: The University of Texas Health Science Center at Houston School of Public Health (HLP, CEB, WC, TMK), Houston, TX.

Address for correspondence: Hsiao Ling Phuar, MSc, BPharm, PhD Candidate, Department of Management, Policy, and Community Health, The University of Texas Health Science Center at Houston School of Public Health, 1200 Pressler Street, Houston, TX 77030. E-mail: Hsiao.Ling.Phuar@uth.tmc.edu

Abstract

Background: For chronic myeloid leukemia (CML) patients, tyrosine kinase inhibitor (TKI) adherence is crucial in achieving optimal response. The study examines the association among TKI out-of-pocket costs, adherence, and healthcare costs and utilization in a large group of commercially insured CML patients.

Methods: CML patients aged 18 to 64 were identified using IBM® MarketScan® Commercial Database between 4/1/2011 and 12/31/2014. Patients were required to

be continuously enrolled 3 months before and 12 months following TKI (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) initiation. TKI adherence is estimated using the proportion of days covered (PDC), defined as the percentage of the proportion of days covered by the prescription fill during the 12-month study period (adherent patients have PDC≥80%). Healthcare cost differences between adherent and non-adherent patients were estimated using generalized linear models. Healthcare utilization was compared using negative binomial regression models. All models were controlled for potential confounding factors.

Results: The study sample consisted of 867 patients, where 357 (41.2%) patients were classified as adherent. Patients with higher TKI out-of-pocket costs (≥75th percentile in the distribution of costs) for a 30-day supply have lower predicted PDC by 2.4% ($p<0.001$). Over the study period, non-adherent patients incurred $10,985 more in medical costs ($p<0.001$), and $1,642 more in non-TKI pharmacy costs ($p<0.01$). Adherent patients incurred $29,061 more in TKI pharmacy costs ($p<0.001$) that resulted in $19,222 more in overall total healthcare cost ($p<0.001$). Adherent patients, however, were estimated to be less likely to have all-cause hospitalizations (IRR=0.32; $p<0.001$), or CML-specific hospitalizations (IRR=0.30; $p<0.01$).

Conclusions: CML patients with lower TKI out-of-pocket costs were more adherent and experienced fewer hospitalizations, resulting in medical service cost savings. These lower medical costs, however, were more than offset by higher TKI medication costs observed during the first year of TKI therapy.

Keywords: Adherence – Chronic myeloid leukemia – Cost – Tyrosine kinase inhibitor – Utilization

Introduction

In the United States, cancer comes in second among all causes of death after heart disease.[1] However, more Americans are surviving cancer over a 10-year period with current statistics showing approximately 15.5 million cancer survivors in January 2016[2] in comparison to 11.4 million in January 2006,[3] reflecting improvements in treatment and earlier diagnosis[2]. Much anticancer drug development has focused on targeted therapies.[4] The use of targeted therapies in cancer grew from 11% in 2003 to 46% in 2013[5] because additional indications for such drugs approved in the early 2000's led to their increased uptake, affecting the use of traditional cytotoxic and hormonal therapies[6]. Tyrosine kinase inhibitors (TKIs) are considered to be the most successful class of targeted cancer therapies, exceeding all survival expectations.[7]

Chronic myeloid leukemia (CML) accounts for 15% of adult leukemias.[8] CML occurs in three different phases (chronic, accelerated, and blast phase), and is usually diagnosed in the chronic phase.[8] Untreated chronic phase CML will eventually progress to advanced phase in 3 to 5 years.[9] Imatinib, dasatinib, and nilotinib are recommended as first-line TKI therapy for newly diagnosed patients with chronic phase CML, followed by bosutinib and ponatinib as second line options.[8,10,11] Imatinib [Gleevec, Novartis], was the first TKI approved by the US Food and

Drug Administration (FDA) for CML treatment in 2001, followed by dasatinib [Sprycel, Bristol-Myers Squibb] in 2006, nilotinib [Tasigna, Novartis] in 2007, and bosutinib [Bosulif, Pfizer] and ponatinib [Iclusig, Ariad Pharmaceuticals] in 2012. [12]

TKIs play a large part in more than doubling the 5-year survival rate for CML over the past two decades, from 31% for patients diagnosed in the early 1990's to 66% for those diagnosed from 2006 to 2012. [2] The median survival used to be 4 to 6 years, but most CML patients treated with TKIs experience near normal life expectancy, particularly those diagnosed before age 65 years. [13,14] Treating CML with TKIs has differentiated the condition from solid cancers, turning it into a chronic, manageable disease similar to diabetes, hypertension, and cardiovascular disorders. [7,10] Patients are required to continuously take their oral TKIs daily to produce the anticipated benefit of long-term survival. [10,11] In addition, adherence to TKI therapy is crucial in achieving optimal response and remaining free of disease progression. [15-17] Several studies have demonstrated that treatment interruptions and non-adherence contribute to failure to achieve complete cytogenetic response (CCyR) [15-17], major molecular response (MMR) [16], and complete molecular response (CMR) [15,16].

Much attention has been focused on the high cost of TKIs and whether these costs inhibit patient use. [7] In the United States, patients may pay an average of 20% of drug prices out-of-pocket [$20,000 - $30,000 per year, a quarter to a third of an average household budget]. [7] Previous studies have shown that increased cost sharing reduces the use of and adherence to prescription drugs. [18,19] One study that

examined patient out-of-pocket expenditures in CML patients using imatinib found that patients with higher spending were 42% more likely to be non-adherent and 70% more likely to discontinue their TKI therapy. [20]

In this study, we examined the association between patient cost sharing with TKI adherence, and also the impact of TKI adherence on subsequent healthcare utilization and costs in commercially insured patients with newly diagnosed CML. We are comprehensively studying the relationships among out-of-pocket costs, adherence, and healthcare utilization or costs for new TKI users in a single study. This study documents how non-adherence in treatment impacts healthcare utilization and overall healthcare costs. Our study measured actual healthcare utilization and costs to determine the effects on utilization patterns and direct healthcare costs.

Methods

Data Source

We used the IBM® MarketScan® Commercial Database from January 1, 2011 to December 31, 2015. The MarketScan database provides inpatient, outpatient, and pharmacy claims data from employer-based, commercially insured group health plans in the United States, covering subscribers and dependents up to age 65. All data were de-identified in accordance with the Health Insurance Portability and Accountability Act (HIPAA) requirements.

Sample Selection

We identified newly diagnosed CML patients with at least one prescription claim for any of the five TKIs (imatinib, dasatinib, nilotinib, bosutinib, and ponatinib) between April 1, 2011, and December 31, 2014 (Figure 3). All these TKIs were approved by the FDA for the treatment of CML and were available during the study period. The first observed TKI dispensing date was considered the index claim. New users of TKIs were defined as having no TKI prescription claims for at least 3 months before the index claim.

Patients were included if they were diagnosed with CML within twelve months prior to the index claim. CML diagnosis is defined using International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code for chronic myeloid leukemia (205.1X) or International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM] code for chronic myeloid leukemia (C92.1X).

Patients were excluded if they were a) younger than age 18 years at index claim date, or turned 65 during the study period, and had b) no continuous enrollment in the health plan and drug benefit in the 3 months before and 12 months after the index claim (pre-index period and post-index period, respectively).

Study Variables

Measure for TKI out-of-pocket costs. We calculated the mean out-of-pocket costs

for a 30-day supply of TKI medication. Out-of-pocket costs were defined as the sum of the copayments, coinsurance, and deductibles paid by the patient at the time that the TKI prescription was filled over the 12-month post-index period. We adjusted out-of-pocket cost amounts for 60- or 90-day prescriptions to 30-day amounts. We used the mean out-of-pocket costs per patient across repeated TKI prescriptions dispensed in the 12-month post-index period and other patient characteristics to predict TKI adherence.

Measure for TKI adherence. We estimated patient's adherence to TKI using the proportion of days covered (PDC).[21] The PDC calculation is based on the fill dates and number of days supply for each fill of a prescription. The numerator is the total number of days covered by the prescription fill during the 12-month post-index period.

The sample was selected on the basis of imatinib, dasatinib, nilotinib, bosutinib, or ponatinib initiation for CML treatment, but the adherence measure included adherence to any TKI used during the study period since patients may have been switched to another TKI (dasatinib, nilotinib, bosutinib, or ponatinib) because of intolerance or failure to respond to the first TKI used. Patients were counted as using a TKI for any day during which they had TKIs available during the post-index period. If a person had overlapping supply of more than one TKI (e.g., he or she filled a prescription for nilotinib before exhausting their supply of imatinib), then use of the second medication was assumed to start the day after the end of the prior fill.

The denominator is 365, the number of days between the index claim and the end of the 12-month post-index period. The ratio was multiplied by 100 to obtain the percentage of the proportion of days covered. Patients were classified as adherent to TKIs if the PDC is greater than or equal to 80%. Clinical benefits are most likely to occur when this threshold is exceeded. [15-17]

Outcomes

Annual healthcare utilization. We assessed healthcare utilization during the 12-month post-index period, using five distinct utilization measures: (1) number of outpatient physician visits; (2) number of emergency room [ER] visits; (3) number of all-cause hospitalizations; (4) number of CML-specific hospitalizations (identified as any inpatient admission with an ICD-9-CM or ICD-10-CM code for CML as the primary or secondary diagnosis); and (5) number of prescriptions.

Annual healthcare costs. We examined total direct healthcare costs during the 12-month post-index period. We used the allowed amount to reflect direct costs, which is the sum of plan paid, Coordination of Benefits and Other Savings (COB), and patient out-of-pocket costs, including copayments, coinsurance, and deductibles. We reported four distinct cost variables: (1) medical costs; (2) TKI pharmacy costs; (3) non-TKI pharmacy costs; and (4) total all-cause healthcare costs.

Medical costs included costs associated with any inpatient or outpatient encounter during the 12-month post-index period regardless of whether visits were

related to CML or TKI-related toxicities. TKI pharmacy costs included costs associated with pharmacy claims for imatinib, dasatinib, nilotinib, bosutinib, and ponatinib during the 12-month post-index period. Non-TKI pharmacy costs incorporated costs associated with any other pharmacy claims not included in the TKI pharmacy related cost calculation. We converted costs ($US) to 2015 values using the medical component of the Consumer Price Index.

Covariates

We reported patient demographic characteristics as of the index claim date, such as patient age, sex, year of the index claim, region of residence (Northeast, North Central, South, West), and the patient's relationship to subscriber (subscriber versus spouse or dependent). To account for possible changes in the patient's health plan type (comprehensive, preferred provider organization [PPO], point-of-service [POS], consumer-driven health plan/high deductible health plan [CDHP/HDHP], exclusive provider organization [EPO], health maintenance organization [HMO]) during the 12-month post-index period, the plan type that the patient had for most part of the year was determined to be the plan type under which the patient was categorized.

We identified clinical characteristics using all available medical and pharmacy claims for study patients in the 3-month pre-index period. These included Deyo-Charlson comorbidity index as a measure of comorbidity burden, [22] the number of unique drug classes filled as a measure of pill burden, and Darkow CML Complexity

Index score (categorized as usual, moderate, or high, using reported diagnoses of associated complications, comorbidities, or adverse events) as a measure of the difficulty of managing patient's disease [23]. We used the starting dose of the index TKI medication as a proxy for the phase of CML disease. [23,24] We calculated this dose as the strength of TKI dispensed multiplied by the quantity filled, divided by the days' supply on the pharmacy claim. For imatinib, the starting dose was categorized as ≤400mg [i.e., the typical starting dose for chronic phase CML] or ≥600mg [i.e., the typical starting dose for accelerated phase or blast crisis]. [25] For dasatinib, the starting dose was categorized as ≤100mg [i.e., the typical starting dose for chronic phase CML] or ≥140mg [i.e., the typical starting dose for advanced phase]. [26] For nilotinib, the starting dose was categorized as ≤600mg [i.e., the typical starting dose for chronic phase CML] or ≥800mg [i.e., the typical starting dose for accelerated phase]. [27] For bosutinib, the starting dose was categorized as ≤500mg [i.e., the typical starting dose for chronic, accelerated, or blast phase CML in patients resistant to or intolerant to other therapies, including imatinib]. [28] For ponatinib, the starting dose was categorized as ≤45mg [i.e., the typical starting dose for chronic, accelerated, or blast phase CML in patients for whom no other TKI therapy is indicated]. [29]

An indicator variable for whether the patient had any TKI dose decrease was used as a proxy for TKI adverse events during the 12-month post-index period because TKI toxicities are managed by decreasing the initial dose prescribed. [8] The

other control variable included was mean other out-of-pocket costs paid by the patient for inpatient and outpatient services, and pharmacy medications (excluding TKI medication) for the entire 12-month post-index period.

Statistical Analyses

Statistical comparisons between the characteristics of patients who were adherent to TKI therapy (PDC≥80%) and patients who were non-adherent to TKI therapy (PDC<80%) were conducted using the Wilcoxon-Mann-Whitney test for continuous variables, and Pearson's chi-squared test or the Fisher's exact test (if one or more cells have an expected frequency of five or less) for categorical variables.

Adherence. The odds of being adherent to TKI versus being non-adherent in a 12-month period was determined using a multivariate logistic regression model with robust standard error estimates, controlling for potential confounding factors. The adjusted risk ratio (ARR) and adjusted risk difference (ARD) were computed instead of odds ratio since adherence was not considered to be a rare event. [30] The ARR is the ratio of the mean predicted probabilities, [31] and denotes the probability of adherence for each category of TKI out-of-pocket costs after controlling for potential confounding factors. The ARD is the difference of the mean predicted probabilities, [31] and indicates differences in the absolute risk of adherence.

Healthcare utilization and costs. We compared healthcare utilization between the

adherent and non-adherent patient cohorts using unadjusted and adjusted incidence rate ratios (IRRs). Adjusted IRRs controlled for potential confounding factors and were estimated using multivariate negative binomial regression models [32]. We did not require the inclusion of any offset variable because we observed all outcome variables for one full year. We estimated unadjusted and adjusted cost differences between the adherent and non-adherent patient cohorts using multivariate generalized linear models with a gamma distribution and a log link, [23] controlling for potential confounding factors.

All statistical analyses were performed using STATA version 15 (StataCorp LP, College Station, Texas). Statistical significance was assumed at p-values less than 0.05. The study protocol was considered exempt by The University of Texas Health Science Center at Houston Institutional Review Board.

Results

Patient characteristics

867 patients were identified in the MarketScan database who were aged 18-64 years and initiated TKI therapy following a new diagnosis of CML between April 1, 2011 and December 31, 2014. 45.9% of patients were on imatinib, 31.9% on dasatinib, 21.8% on nilotinib, 0.2% on bosutinib, and 0.2% on ponatinib (Table 5). Among this cohort, 58.8% of patients were non-adherent because they had fewer than 80% of TKI medication days covered (PDC<80%) during the first year of therapy.

The mean ages of adherent and non-adherent patients were 51 years and 47 years, respectively. Most of the non-adherent patients were in the 18-39 (72.2%), 40-49 (64.7%), and 50-59 (51.7%) age groups, whereas the 60-64 age group had more adherent patients (52.2%). 57.4% of adherent and 51.4% of non-adherent patients were male, but the difference was not statistically significant (p=0.08). The majority were enrolled in group health plans with richer benefits, which include comprehensive, PPO, POS, and EPO, as shown by 75.6% of adherent and 73.9% of non-adherent patients. Most patients also lived in the south; 37.0% of adherent patients and 46.7% of non-adherent patients, and this is an inherent characteristic of patients in the MarketScan data set.

Adherent patients initiated TKI therapy relatively quicker compared to non-adherent patients (37 days versus 67 days). More than 70% of patients who initiated TKI after 3 months of CML diagnosis were non-adherent. Most patients were in the chronic phase of CML; 94.4% of adherent patients and 86.9% of non-adherent patients, respectively. 89.6% of adherent patients and 84.7% of non-adherent patients did not switch TKI, whereas 87.4% of adherent patients and 82.3% of non-adherent patients did not have any TKI dose decrease during the 12-month post-index period. 52.7% of adherent patients reported having usual Darkow CML Complexity Index scores compared to 64.1% of non-adherent patients. The 10 most prevalent comorbidities found in the study cohorts are reported in Table 5.

The mean out-of-pocket costs for a 30-day supply of TKI medication were

$126.77 (SD=234.29) for adherent patients and $188.48 (SD=639.07) for non-adherent patients, but the difference was not statistically significant (p=0.08). The mean annual total of other out-of-pocket costs were $1,730.62 (SD=1,541.22) and $1,848.22 (SD=1,892.38) for adherent and non-adherent patients, respectively, but the difference was also not statistically significant (p=0.98).

In the unadjusted analysis, adherence to TKI was associated with out-of-pocket costs for TKI therapy, patient age, region of residence, index year of TKI initiation, time to TKI drug index date from CML diagnosis date, index treatment, the phase of CML disease, any TKI dose decrease, the Darkow CML Complexity Index score, and concomitant medications.

Factors associated with TKI adherence

Out-of-pocket costs for TKI medication. We found that 30-day out-of-pocket costs for TKI medication were significantly associated with the adjusted risk of adherence (p<0.01). On average, copayments accounted for approximately 78.9% of the total out-of-pocket costs for a 30-day supply of TKI medication, while coinsurance and deductibles accounted for 11.8% and 9.3%, respectively.

Most patients (64.7%) have mean monthly out-of-pocket costs for TKI medication above $0 and below $100. There is a positive association for each increased category of out-of-pocket costs for TKI medication, controlling for potential confounding factors until the highest category of out-of-pocket costs was reached

(Table 6). On average, patients with a mean monthly out-of-pocket cost for TKI medication above $400 were 1% less likely to be adherent to TKI compared to patients with no out-of-pocket costs, after controlling for potential confounding factors (95% CI, 0.66 to 1.47). In general, patients with higher TKI out-of-pocket costs (≥75th percentile in the distribution of costs) that amounted to $100 or more for a 30-day supply have lower predicted PDC by 2.4% ($p<0.001$).

Other patient characteristics. Older patients were more likely to be adherent to TKI compared to younger patients as shown by each increased category of patient age (60-64 versus 18-39: ARR, 1.60; 95% CI, 1.32-1.94; 50-59 versus 18-39: ARR, 1.61; 95% CI, 1.33-1.96). Patients in the geographical North Central and West regions of the United States were significantly more likely to be adherent to TKI compared to patients in the South (North Central: ARR, 1.25; 95% CI, 1.04 to 1.50; West: ARR, 1.33; 95% CI, 1.10 to 1.61).

Patients with more time between CML diagnosis date and TKI drug index claim date were less likely to be adherent to TKI (10-12 months versus 0-3 months: ARR, 0.48; 95% CI, 0.25 to 0.94; 7-9 months versus 0-3 months: ARR, 0.47; 95% CI, 0.22 to 1.04; 4-6 months versus 0-3 months: ARR, 0.61; 95% CI, 0.45 to 0.83). Patients who were taking dasatinib and nilotinib were significantly more likely to be adherent than patients taking imatinib (dasatinib: ARR, 1.25; 95% CI, 1.06 to 1.48; nilotinib: ARR, 1.20; 95% CI, 1.00 to 1.45). Patients who had chronic phase CML were also significantly more likely to be adherent compared to patients who were in

the advanced phase (ARR, 1.49; 95% CI, 1.04 to 2.13). Patients who had their TKI doses decreased (as a proxy for TKI adverse events) were significantly less likely to be adherent to TKI (ARR, 0.75; 95% CI, 0.59 to 0.95). Patients who had high Darkow CML Complexity Index were significantly more likely to be adherent compared to patients who had the usual complexity (ARR, 1.22; 95% CI, 1.00 to 1.48). Patients were less likely to be adherent to TKI for every increase in pre-existing condition that they had (ARR, 0.93; 95% CI, 0.89 to 0.99).

Copayments, coinsurance, and deductibles accounted for 44.2%, 29.0%, and 26.8% of total annual out-of-pocket costs for other prescription medication, and inpatient and outpatient services. These other out-of-pocket costs were not associated with adherence to TKI medication ($p>0.05$).

Healthcare utilization and costs

Non-adherent patients were observed to have greater healthcare utilization compared to adherent patients, particularly utilization related to emergency room visits and hospitalizations (Table 7). On an unadjusted basis, adherent patients were estimated to be less likely to have all-cause hospitalizations (IRR=0.25, $p<0.001$), or CML-specific hospitalizations (IRR=0.20, $p<0.001$). Adherent patients, however, were estimated to be more likely to have a higher number of prescriptions (IRR=1.31, $p<0.001$). This was observed in the higher average number of TKI prescriptions (12.6 versus 6.8, $p<0.001$), and higher average number of non-TKI prescriptions (25.8 versus 22.5, $p=0.01$) for adherent patients compared to non-

adherent patients. Adherent patients also had slightly more outpatient physician visits (16.1 versus 15.3, p<0.001). After adjusting for potential confounding factors, adherent patients were estimated to be less likely to have all-cause hospitalizations (IRR=0.32; p<0.001), or CML-specific hospitalizations (IRR=0.30; p<0.01).

Among the components of unadjusted total annual all-cause healthcare costs (adherent patients=$123,033; non-adherent patients=$103,887, p<0.001), TKI pharmacy costs (adherent patients=$108,068; non-adherent patients=$74,045; p<0.001) accounted for 87.8% and 71.3% of these costs, respectively (Table 8). After adjusting for potential confounding factors, adherent patients incurred $19,222 more in total annual healthcare costs (p<0.001). Cost differences were mainly driven by a TKI pharmacy cost difference of $29,061 (p<0.001) that was not offset by the higher medical costs ($10,985, p<0.001) and higher non-TKI pharmacy costs ($1,642, p<0.01) incurred by non-adherent patients.

Discussion

In our study, the average adherence is 69.5% (median=76.4%), which is well within the 69-79% range for proportion of days covered (PDC) reported in studies based on claims data [33]. For our study, we classified patients as adherent to TKIs if they have PDC greater than or equal to 80% because literature shows that clinical benefits are most likely to occur when this threshold is exceeded. [15-17] In our study cohort with 867 patients, 41.2% were found to be adherent in their first year of therapy after being newly diagnosed with CML. This is consistent with studies

showing that 44-97% of CML patients were classified as being adherent to TKIs. [33] These studies reported a wide range of percentages that resulted from using different methods to measure adherence, and the varying cut off (usually in the range of 80-90%) to group adherent and non-adherent patients. [33]

Out-of-pocket costs for the monthly supply of TKI medication averaged $164; median out-of-pocket costs were $50 (range, $0-$9,079). Costs varied substantially among individuals in our sample, with 7.2% having zero out-of-pocket costs, and 10.5% paying more than $300, which is double the estimated average monthly cost. Most patients (64.7%) incurred out-of-pocket costs above $0 and less than $100. In general, we observed that patients with TKI out-of-pocket costs of $100 or more ($\geq 75^{th}$ percentile in the distribution of costs) for their monthly supply have lower predicted PDC by 2.4% ($p<0.001$). This translates to approximately a nine-day difference in days covered. The clinical implications of this non-adherence can be significant, with patients who missed 10% of their daily doses (i.e., 3 days per month) less likely to achieve a major molecular response and more likely to lose cytogenetic response. [16,17,34]

However, when we broke down the TKI out-of-pocket costs for a 30-day supply into proportionate categories, we found a positive association for each increased category of out-of-pocket costs for TKI medication, controlling for potential confounding factors, until the highest category of out-of-pocket costs was reached at $400. Our analyses may be regarded as the best-case scenario when evaluating the

association between patient cost sharing and adherence to TKI because our study population comprised commercially insured patients with relatively generous employer-sponsored insurance (median out-of-pocket costs, $50 per fill) who filled at least one TKI prescription. This may result in our study not capturing patients with very high cost sharing who did not fill the first prescription. In addition, patients in our study cohort are eligible for patient assistance or prescription assistance programs that can help finance their TKI medication costs, allowing them to get their drugs free or at reduced costs. [35] For instance, Novartis Pharmaceuticals Corporation has the universal co-pay card for Gleevec and Tasigna in which patients are responsible for up to the first $25 and the program pays the remaining co-pay or coinsurance until the yearly maximum of $15,000 is reached. [36] Takeda Oncology has the co-pay assistance program for Iclusig that limits patient's co-pay or coinsurance to $10 per month. [36]

Our findings suggest that once patients are initiated on TKI therapy, the monthly out-of-pocket costs that they incurred for their TKI medications may not be a significant predictor of their adherence. We found that factors such as the time to TKI drug index date from CML diagnosis date, and incidence of any TKI dose decrease were significant predictors of adherence. Patients who initiated TKI later than three months after CML diagnosis were significantly associated with 39-53% lower likelihood of adherence to TKI. This was consistent with how a long lag time between CML diagnosis and therapy initiation was associated with higher non-

adherence. [15,37-40] In addition, patients who experienced any adverse effects from the drug (based on observed TKI dose decreases) were significantly associated with 25% lower likelihood of adherence to TKI. This was consistent with other studies that reported patients experiencing adverse effects from the medication were more likely to be non-adherent. [16,33,37,38,41,42]

The main finding is that non-adherent patients experienced higher levels of healthcare utilization. They were more likely to have more frequent hospitalizations, regardless of whether it is CML-specific or otherwise, compared to adherent patients (both $p<0.05$). This is consistent with a previous study reporting that low adherence was associated with more than 10 times higher frequency of inpatient visits compared to patients with high adherence. [43] The more frequent hospitalizations, however, did not convert into higher total all-cause healthcare costs ($p<0.05$) in spite of non-adherent patients incurring higher medical costs and non-TKI pharmacy costs (both $p<0.05$). These were more than offset by higher TKI medications costs incurred by the adherent patients ($p<0.05$). These findings contrast with reports of costly non-pharmacologic medical services due to treatment failures. [43-45]

Our findings have important implications. To the best of our knowledge, this is the first study to research the association between patient cost sharing, adherence to TKI, and subsequent healthcare utilization and costs in a population of commercially insured patients newly diagnosed with CML. Non-adherence to TKI medication may put patients at increased risk of treatment failure due to resistant

CML. [16,17] The success story of TKIs show how effective but expensive novel anticancer drugs will continue improving patient outcomes and expanding treatment options, but patients and insurers are left to bear the increasing financial burden. [46] Despite their high cost, optimal use of TKIs has generated substantial health improvements for CML patients, and can reduce the economic burden of CML for insurers through decreased healthcare utilization. [23,43,46,47] Future research should focus on interventions to improve TKI adherence by exploring the role that physicians and pharmacists can play to ensure that patients are initiated on TKI immediately after a diagnosis of CML. A delay in TKI initiation could decrease adherence that will affect treatment response, which can result in patients requiring stem-cell transplantation, worse clinical outcomes, and potentially shorter life expectancy. [48,49]

The study is subject to some limitations. As with all observational studies, there is the potential for unobserved confounding since our claims data lack certain clinical or treatment history variables, and socioeconomic factors. We used multivariate regressions with proxies found in the literature to control for these unavailable sociodemographic and clinical characteristics to offset the limitations of our observational design. Other limitations common to studies using administrative claims data, such as claims coding errors and missing data, may apply in this study. Nonetheless, claims data have the advantage of being a valid, large-sample source of real-world practice data. [50]

The use of insurance claims data included information on filled prescriptions only. Assessing adherence using prescription claims assumes that patients are taking medications as consistently as they fill their prescriptions. These databases also do not provide information on the reasons for patients to stop their medications (e.g., doctor's advice due to medication side effects or ineffectiveness). In some cases, our results may be underestimating the true adverse impact of high cost sharing if patients have supplemental cost-sharing help from patient assistance programs. Despite these shortcomings, pharmacy and insurance records provide the most accurate estimate of actual medication use in large populations over extended periods of time. [51,52]

We have unequal numbers of patients on the five different TKIs observed in our 5-year study period due to the varying years of TKI approval by the FDA for CML treatment. Imatinib, dasatinib, and nilotinib were the first three TKIs approved by the FDA for CML treatment in 2001, 2006, and 2007, respectively. [12] Bosutinib and ponatinib were relatively new drugs at the time of the study since the FDA approved these two TKIs for CML treatment in 2012. [12] Future research should take into consideration the rapidly evolving landscape of available TKIs and frontline therapy recommendations for treating CML. [48]

Conclusions

Our study suggests that CML patients with lower TKI out-of-pocket costs were more adherent and experienced lower healthcare utilization, resulting in medical

service cost savings. Patients with better adherence were at lower risk of adverse events such as hospitalizations. These lower medical costs, however, were more than offset by higher TKI medication costs observed during the first year of TKI therapy. This research provides critical new evidence to physicians and pharmacists in suggesting that high drug out-of-pocket costs may limit initial access to life-saving oral anticancer medications that subsequently impact patient adherence.

Transparency

Declaration of funding: Not applicable.

Declaration of financial/other relationships: All authors report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Acknowledgment: A poster presentation for this study has been made at the American Public Health Association (APHA) 2018 Annual Meeting and Expo on November 10 – 14, 2018.

References

1. Kochanek KD, Murphy SL, Xu J, Tejada-Vera B. Deaths: Final data for 2014. *Natl Vital Stat Rep*. 2016;65(4):1-122. https://www.cdc.gov/nchs/data/nvsr/nvsr65/nvsr65_04.pdf. Accessed July 5, 2018.

2. American Cancer Society. Cancer facts & figures 2017. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf. Updated 2017. Accessed July 5, 2018.

3. American Cancer Society. Cancer facts & figures 2010. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2010/cancer-facts-and-figures-2010.pdf. Updated 2010. Accessed July 5, 2018.

4. National Cancer Institute. Targeted cancer therapies. https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet. Updated 2018. Accessed July 5, 2018.

5. American Society of Clinical Oncology. The state of cancer care in america, 2015: A report by the american society of clinical oncology. *J Oncol Pract*. 2015;11(2):79-113. http://ascopubs.org/doi/pdf/10.1200/JOP.2015.003772. Accessed July 5, 2018.

6. Johnson K, Blansett L, Mawrie R, Di Biase S. Innovation in cancer care and implications for health systems: Global oncology trend report. *IMS Institute for Healthcare Informatics*. 2014;May. http://allianceforpatientaccess.org/wp-content/uploads/2014/06/IMSH_Oncology_Trend_Report.pdf. Accessed July 5, 2018.

7. Experts in Chronic Myeloid Leukemia. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: From the perspective of a large group of CML experts. *Blood*. 2013;121(22):4439-4442. http://www.bloodjournal.org/content/121/22/4439.full. Accessed June 23, 2018.

8. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Chronic myeloid leukemia. https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. Updated 2018. Accessed June 23, 2018.

9. Sawyers CL. Chronic myeloid leukemia. *N Engl J Med*. 1999;340(17):1330-1340. https://www-nejm-org.utsph.idm.oclc.org/doi/full/10.1056/NEJM199904293401706. Accessed June 23, 2018.

10. Cuellar S, Vozniak M, Rhodes J, Forcello N, Olszta D. BCR-ABL1 tyrosine kinase inhibitors for the treatment of chronic myeloid leukemia. *J Oncol Pharm Pract*. 2017.

http://journals.sagepub.com.utsph.idm.oclc.org/doi/abs/10.1177/1078155217710553. Accessed June 23, 2018.

11. Mathisen MS, Kantarjian HM, Cortes J, Jabbour EJ. Practical issues surrounding the explosion of tyrosine kinase inhibitors for the management of chronic myeloid leukemia. *Blood Rev*. 2014;28(5):179-187. https://www.bloodreviews.com/article/S0268-960X(14)00042-3/fulltext. Accessed June 23, 2018.

12. CenterWatch. FDA approved drugs for oncology. http://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/12/oncology. Updated 2018. Accessed June 26, 2018.

13. National Cancer Institute. Chronic myelogenous leukemia treatment - health professional version. https://www.cancer.gov/types/leukemia/hp/cml-treatment-pdq. Updated 2018. Accessed June 23, 2018.

14. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67:7-30. https://onlinelibrary.wiley.com/doi/10.3322/caac.21387. Accessed June 23, 2018.

15. Noens L, van Lierde MA, De Bock R, et al. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: The ADAGIO study. *Blood*. 2009;113(22):5401-5411.

http://www.bloodjournal.org/content/113/22/5401.short?sso-checked=true. Accessed June 23, 2018.

16. Marin D, Bazeos A, Mahon F, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *J Clin Oncol*. 2010;28(14):2381-2388. http://ascopubs.org/doi/full/10.1200/JCO.2009.26.3087. Accessed June 23, 2018.

17. Ibrahim AR, Eliasson L, Apperley JF, et al. Poor adherence is the main reason for loss of CCyR and imatinib failure for chronic myeloid leukemia patients on long-term therapy. *Blood*. 2011;117(14):3733-3736. http://www.bloodjournal.org/content/117/14/3733. Accessed June 23, 2018.

18. Goldman DP, Joyce GF, Zheng Y. Prescription drug cost sharing: Associations with medication and medical utilization and spending and health. *JAMA*. 2007;298(1):61-69. https://www.researchgate.net/publication/6229235_Prescription_Drug_Cost_Sharing_Associations_With_Medication_and_Medical_Utilization_and_Spending_and_Health. Accessed July 5, 2018.

19. Briesacher BA, Gurwitz JH, Soumerai SB. Patients at-risk for cost-related medication nonadherence: A review of the literature. *J Gen Intern Med*. 2007;22(6):864-871. https://link-springer-com.utsph.idm.oclc.org/article/10.1007/s11606-007-0180-x. Accessed July 5, 2018.

20. Dusetzina SB, Winn AN, Abel GA, Huskamp HA, Keating NL. Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. *J Clin Oncol*. 2013;32(4):306-311. http://ascopubs.org/doi/full/10.1200/JCO.2013.52.9123. Accessed June 26, 2018.

21. Nau DP. Proportion of days covered (PDC) as a preferred method of measuring medication adherence. *Springfield, VA: Pharmacy Quality Alliance*. 2012. http://ep.yimg.com/ty/cdn/epill/pdcmpr.pdf. Accessed June 23, 2018.

22. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619. https://www-sciencedirect-com.utsph.idm.oclc.org/science/article/pii/0895435692901338. Accessed June 23, 2018.

23. Darkow T, Henk HJ, Thomas SK, et al. Treatment interruptions and non-adherence with imatinib and associated healthcare costs. *Pharmacoeconomics*. 2007;25(6):481-496. https://link-springer-com.utsph.idm.oclc.org/article/10.2165/00019053-200725060-00004. Accessed June 23, 2018.

24. Ward MA, Fang G, Richards KL, et al. Comparative evaluation of patients newly initiating first-generation versus second-generation tyrosine kinase inhibitors for chronic myeloid leukemia and medication adherence, health services utilization, and

healthcare costs. *Curr Med Res Opin*. 2015;31(2):289-297. https://www-tandfonline-com.utsph.idm.oclc.org/doi/abs/10.1185/03007995.2014.991440. Accessed June 25, 2018.

25. Medscape. Imatinib (rx). http://reference.medscape.com/drug/gleevec-imatinib-342239. Updated 2018. Accessed June 23, 2018.

26. Medscape. Dasatinib (rx). http://reference.medscape.com/drug/sprycel-dasatinib-342199. Updated 2018. Accessed June 23, 2018.

27. Medscape. Nilotinib (rx). http://reference.medscape.com/drug/tasigna-nilotinib-342198. Updated 2018. Accessed June 23, 2018.

28. Medscape. Bosutinib (rx). http://reference.medscape.com/drug/bosulif-bosutinib-999770. Updated 2018. Accessed June 23, 2018.

29. Medscape. Ponatinib (rx). http://reference.medscape.com/drug/iclusig-ponatinib-999800. Updated 2018. Accessed June 23, 2018.

30. Kleinman LC, Norton EC. What's the risk? A simple approach for estimating adjusted risk measures from nonlinear models including logistic regression. *Health Serv Res*. 2009;44(1):288-302. https://www-ncbi-nlm-nih-gov.utsph.idm.oclc.org/pmc/articles/PMC2669627/. Accessed July 5, 2018.

31. Norton EC, Miller MM, Kleinman LC. Computing adjusted risk ratios and risk differences in stata. *Stata J*. 2013;13(3):492-509. https://pdfs.semanticscholar.org/28cb/e7852bb3d11c5e9518c0a7a06ce022a89ccb.pdf. Accessed July 5, 2018.

32. UCLA Institute for Digital Research and Education. Regression models with count data. https://stats.idre.ucla.edu/stata/seminars/regression-models-with-count-data/. Updated 2018. Accessed July 6, 2018.

33. Noens L, Hensen M, Kucmin-Bemelmans I, Lofgren C, Gilloteau I, Vrijens B. Measurement of adherence to BCR-ABL inhibitor therapy in chronic myeloid leukemia: Current situation and future challenges. *Haematologica*. 2014;99(3):437-447. http://www.haematologica.org.utsph.idm.oclc.org/content/99/3/437.short. Accessed July 6, 2018.

34. Santoleri F, Lasala R, Ranucci E, et al. Medication adherence to tyrosine kinase inhibitors: 2-year analysis of medication adherence to imatinib treatment for chronic myeloid leukemia and correlation with the depth of molecular response. *Acta Haematol*. 2016;136(1):45-51.

35. Leukemia & Lymphoma Society. Financial support. https://www.lls.org/support/financial-support. Updated 2018. Accessed November 7, 2018.

36. RxAssist. Provider center. https://www.rxassist.org/providers. Updated 2018. Accessed November 7, 2018.

37. Jabbour E, Saglio G, Radich J, Kantarjian H. Adherence to BCR-ABL inhibitors: Issues for CML therapy. *Clin Lymphoma Myeloma Leuk*. 2012;12(4):223-229. https://www.clinical-lymphoma-myeloma-leukemia.com/article/S2152-2650(12)00056-0/fulltext. Accessed June 23, 2018.

38. Hall AE, Paul C, Bryant J, et al. To adhere or not to adhere: Rates and reasons of medication adherence in hematological cancer patients. *Crit Rev Oncol*. 2016;97:247-262. https://www.croh-online.com/article/S1040-8428(15)30040-8/fulltext. Accessed June 23, 2018.

39. Henk HJ, Woloj M, Shapiro M, Whiteley J. Real-world analysis of tyrosine kinase inhibitor treatment patterns among patients with chronic myeloid leukemia in the united states. *Clin Ther*. 2015;37(1):124-133. https://www.clinicaltherapeutics.com/article/S0149-2918(14)00692-4/fulltext. Accessed June 23, 2018.

40. StCharles M, Bollu VK, Hornyak E, Coombs J, Blanchette CM, DeAngelo DJ. Predictors of treatment non-adherence in patients treated with imatinib mesylate for chronic myeloid leukemia. *Blood*. 2009;114(22):2209. http://www.bloodjournal.org/content/114/22/2209. Accessed June 23, 2018.

41. Eliasson L, Clifford S, Barber N, Marin D. Exploring chronic myeloid leukemia patients' reasons for not adhering to the oral anticancer drug imatinib as prescribed. *Leuk Res*. 2011;35(5):626-630. https://www-sciencedirect-com.utsph.idm.oclc.org/science/article/pii/S0145212610005102. Accessed July 6, 2018.

42. Efficace F, Rosti G, Cottone F, et al. Profiling chronic myeloid leukemia patients reporting intentional and unintentional non-adherence to lifelong therapy with tyrosine kinase inhibitors. *Leuk Res*. 2014;38(3):294-298. https://www-sciencedirect-com.utsph.idm.oclc.org/science/article/pii/S0145212613002300. Accessed July 6, 2018.

43. Wu EQ, Johnson S, Beaulieu N, et al. Healthcare resource utilization and costs associated with non-adherence to imatinib treatment in chronic myeloid leukemia patients. *Curr Med Res Opin*. 2010;26(1):61-69. https://www-tandfonline-com.utsph.idm.oclc.org/doi/abs/10.1185/03007990903396469. Accessed June 23, 2018.

44. Knopf KB, Divino V, McGarry L, et al. Economic burden of tyrosine kinase inhibitor treatment failure in chronic myeloid leukemia. *Clin Lymphoma Myeloma Leuk*. 2015;15(11):e163-e171. https://www.clinical-lymphoma-myeloma-leukemia.com/article/S2152-2650(15)01079-4/fulltext. Accessed June 25, 2018.

45. McGarry LJ, Chen YJ, Divino V, et al. Increasing economic burden of tyrosine kinase inhibitor treatment failure by line of therapy in chronic myeloid leukemia. *Curr Med Res Opin*. 2016;32(2):289-299. https://www-tandfonline-com.utsph.idm.oclc.org/doi/abs/10.1185/03007995.2015.1120189. Accessed June 25, 2018.

46. Darkow T, Maclean JR, Joyce GF, Goldman D, Lakdawalla DN. Coverage and use of cancer therapies in the treatment of chronic myeloid leukemia. *Am J Manag Care*. 2012;18:S272-S278. https://www.ajmc.com/journals/supplement/2012/a386_12nov_oncology/a386_12nov_onclogy_darkow_s272to78?p=1. Accessed July 6, 2018.

47. Kropf P, Barnes G, Tang B, Pathak A, Issa JJ. Healthcare utilization and costs associated with tyrosine kinase inhibitor switching in patients with chronic myeloid leukemia. *Leuk Lymphoma*. 2016;57(4):935-941. https://www-tandfonline-com.utsph.idm.oclc.org/doi/abs/10.3109/10428194.2015.1088654. Accessed July 6, 2018.

48. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2018 update on diagnosis, therapy and monitoring. *Am J Hematol*. 2018;93(3):442-459. https://onlinelibrary-wiley-com.utsph.idm.oclc.org/doi/full/10.1002/ajh.25011. Accessed June 26, 2018.

49. Jabbour EJ, Kantarjian H, Eliasson L, Megan Cornelison A, Marin D. Patient adherence to tyrosine kinase inhibitor therapy in chronic myeloid leukemia. *Am J*

Hematol. 2012;87(7):687-691. https://onlinelibrary-wiley-com.utsph.idm.oclc.org/doi/full/10.1002/ajh.23180. Accessed June 26, 2018.

50. Wu EQ, Guerin A, Yu AP, Bollu VK, Guo A, Griffin JD. Retrospective real-world comparison of medical visits, costs, and adherence between nilotinib and dasatinib in chronic myeloid leukemia. *Curr Med Res Opin*. 2010;26(12):2861-2869. https://www-tandfonline-com.utsph.idm.oclc.org/doi/abs/10.1185/03007995.2010.533648. Accessed June 25, 2018.

51. Partridge AH, Avorn J, Wang PS, Winer EP. Adherence to therapy with oral antineoplastic agents. *J Natl Cancer Inst*. 2002;94(9):652-661. https://academic-oup-com.utsph.idm.oclc.org/jnci/article/94/9/652/2520164. Accessed July 5, 2018.

52. Ruddy K, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. *CA Cancer J Clin*. 2009;59(1):56-66. https://onlinelibrary-wiley-com.utsph.idm.oclc.org/doi/full/10.3322/caac.20004. Accessed July 5, 2018.

Table 5: Baseline Characteristics of Patients Newly Diagnosed With CML Receiving TKI Therapy

	Total number of patients (n = 867)	Patient who are non-adherent to TKI therapy (PDC < 80%) (n = 510)	Percent non-adherent[a]	Patient who are adherent to TKI therapy (PDC ≥ 80%) (n = 357)	Percent adherent[a]	p-value[b]
Demographic characteristics						
Age at the index date, years, mean±SD [median]	48.38±11.05 [51]	46.67±11.26 [49]		50.82±10.28 [53]		<0.001[c]
Age group, years, n						<0.001[c]
18 – 39	187 (21.6%)	135 (26.5%)	72.2%	52 (14.6%)	27.8%	
40 – 49	221 (25.5%)	143 (28.0%)	64.7%	78 (21.8%)	35.3%	
50 – 59	323 (37.2%)	167 (32.7%)	51.7%	156 (43.7%)	48.3%	
60 – 64	136 (15.7%)	65 (12.8%)	47.8%	71 (19.9%)	52.2%	
Male, n	467 (53.9%)	262 (51.4%)	56.1%	205 (57.4%)	43.9%	0.08
Patient's relationship to subscriber, n						0.46
Subscriber	568 (65.5%)	329 (64.5%)	57.9%	239 (66.9%)	42.1%	
Spouse or dependent	299 (34.5%)	181 (35.5%)	60.5%	118 (33.1%)	39.5%	
Health plan type, n						0.12
Group: Comprehensive / Preferred provider organization / Point-of-service / Exclusive provider	647 (74.6%)	377 (73.9%)	58.3%	270 (75.6%)	41.7%	

	Total number of patients (n = 867)	Patient who are non-adherent to TKI therapy (PDC < 80%) (n = 510)	Percent non-adherent[a]	Patient who are adherent to TKI therapy (PDC ≥ 80%) (n = 357)	Percent adherent[a]	p-value[b]
organization						
Consumer-driven health plan / high deductible health plan	85 (9.8%)	47 (9.2%)	55.3%	38 (10.6%)	44.7%	
Health maintenance organization	96 (11.1%)	56 (11.0%)	58.3%	40 (11.2%)	41.7%	
Missing / Unknown	39 (4.5%)	30 (5.9%)	76.9%	9 (2.5%)	23.1%	
Region of residence, n						0.03[c]
Northeast	165 (19.0%)	96 (18.8%)	58.2%	69 (19.3%)	41.8%	
North Central	177 (20.4%)	94 (18.4%)	53.1%	83 (23.3%)	46.9%	
South	370 (42.7%)	238 (46.7%)	64.3%	132 (37.0%)	35.7%	
West	139 (16.0%)	71 (13.9%)	51.1%	68 (19.0%)	48.9%	
Unknown	16 (1.8%)	11 (2.2%)	68.8%	5 (1.4%)	31.3%	
Index year, n						0.04[c]
2011	298 (34.4%)	192 (37.6%)	64.4%	106 (29.7%)	35.6%	
2012	200 (23.1%)	121 (23.7%)	60.5%	79 (22.1%)	39.5%	
2013	204 (23.5%)	108 (21.2%)	52.9%	96 (26.9%)	47.1%	
2014	165 (19.0%)	89 (17.5%)	53.9%	76 (21.3%)	46.1%	
Time to drug index date from diagnosis date, days, mean±SD	54.31±73.30 [21]	66.99±81.46 [27.5]		36.18±54.99 [15]		<0.001[c]

	Total number of patients (n = 867)	Patient who are non-adherent to TKI therapy (PDC < 80%) (n = 510)	Percent non-adherent[a]	Patient who are adherent to TKI therapy (PDC ≥ 80%) (n = 357)	Percent adherent[a]	p-value[b]
[median]						
Time group, months, n						<0.001[c]
0 – 3	689 (79.5%)	373 (73.1%)	54.1%	316 (88.5%)	45.9%	
4 – 6	115 (13.3%)	85 (16.7%)	73.9%	30 (8.4%)	26.1%	
7 – 9	30 (3.5%)	25 (4.9%)	83.3%	5 (1.4%)	16.7%	
10 – 12	33 (3.8%)	27 (5.3%)	81.8%	6 (1.7%)	18.2%	
Index treatment, n						<0.001[c]
Imatinib						
Started on ≤400 mg/day	360 (41.5%)	227 (44.5%)	63.1%	133 (37.2%)	36.9%	
Started on ≥600 mg/day	38 (4.4%)	31 (6.1%)	81.6%	7 (2.0%)	18.4%	
Dasatinib						
Started on ≤100 mg/day	265 (30.6%)	133 (26.1%)	50.2%	132 (37.0%)	49.8%	
Started on ≥140 mg/day	11 (1.3%)	9 (1.8%)	81.8%	2 (0.6%)	18.2%	
Nilotinib						
Started on ≤600 mg/day	155 (17.9%)	83 (16.3%)	53.5%	72 (20.2%)	46.5%	
Started on ≥800 mg/day	34 (3.9%)	25 (4.9%)	73.5%	9 (2.5%)	26.5%	

	Total number of patients (n = 867)	Patient who are non-adherent to TKI therapy (PDC < 80%) (n = 510)	Percent non-adherent[a]	Patient who are adherent to TKI therapy (PDC ≥ 80%) (n = 357)	Percent adherent[a]	p-value[b]
Bosutinib						
Started on ≤500mg/day	2 (0.2%)	1 (0.2%)	50.0%	1 (0.3%)	50.0%	
Ponatinib						
Started on ≤45mg/day	2 (0.2%)	1 (0.2%)	50.0%	1 (0.3%)	50.0%	
CML chronic phase, n	780 (90.0%)	443 (86.9%)	56.8%	337 (94.4%)	43.2%	<0.001[c]
Any switching of TKI, n						0.04[c]
Yes	115 (13.3%)	78 (15.3%)	67.8%	37 (10.4%)	32.2%	
No	752 (86.7%)	432 (84.7%)	57.4%	320 (89.6%)	42.6%	
Any TKI dose decrease, n						0.04[c]
Yes	135 (15.6%)	90 (17.7%)	66.7%	45 (12.6%)	33.3%	
No	732 (84.4%)	420 (82.3%)	57.4%	312 (87.4%)	42.6%	
Darkow CML Complexity Index, n						<0.01[c]
Usual	515 (59.4%)	327 (64.1%)	63.5%	188 (52.7%)	36.5%	
Moderate	208 (24.0%)	112 (22.0%)	53.8%	96 (26.9%)	46.2%	
High	144 (16.6%)	71 (13.9%)	49.3%	73 (20.4%)	50.7%	
Deyo-Charlson comorbidity index, mean±SD [median]	2.39±1.14 [2]	2.39±1.25 [2]		2.38±0.96 [2]		0.33

	Total number of patients (n = 867)	Patient who are non-adherent to TKI therapy (PDC < 80%) (n = 510)	Percent non-adherent[a]	Patient who are adherent to TKI therapy (PDC ≥ 80%) (n = 357)	Percent adherent[a]	p-value[b]
10 most prevalent comorbidities, n[d]						-[d]
Diabetes	93 (10.7%)	57 (11.2%)	61.3%	36 (10.1%)	38.7%	
Chronic obstructive pulmonary	55 (6.3%)	30 (5.9%)	54.5%	25 (7.0%)	45.5%	
Acute myocardial	17 (2.0%)	13 (2.6%)	76.5%	4 (1.1%)	23.5%	
Renal	16 (1.8%)	9 (1.8%)	56.3%	7 (2.0%)	43.8%	
Cerebrovascular	15 (1.7%)	5 (1.0%)	33.3%	10 (2.8%)	66.7%	
Metastatic cancer	15 (1.7%)	12 (2.4%)	80.0%	3 (0.8%)	20.0%	
Congestive heart	13 (1.5%)	8 (1.6%)	61.5%	5 (1.4%)	38.5%	
Rheumatoid disease	11 (1.3%)	7 (1.4%)	63.6%	4 (1.1%)	36.4%	
Diabetes with complications	11 (1.3%)	4 (0.8%)	36.4%	7 (2.0%)	63.6%	
Peripheral vascular	7 (0.8%)	4 (0.8%)	57.1%	3 (0.8%)	42.9%	
Concomitant medications / Number of unique drug classes, mean±SD [median]	4.80±3.36 [4]	4.50±3.28 [4]		5.23±3.42 [5]		<0.001[c]
Out-of-pocket costs for a 30-day supply of TKI medication, mean±SD	163.07±513.35 [49.39]	188.48±639.07 [45.07]		126.77±234.29 [55.81]		0.08

	Total number of patients (n = 867)	Patient who are non-adherent to TKI therapy (PDC < 80%) (n = 510)	Percent non-adherent[a]	Patient who are adherent to TKI therapy (PDC ≥ 80%) (n = 357)	Percent adherent[a]	p-value[b]
[median]						
Out-of-pocket costs group, n						<0.05[c]
$0	62 (7.2%)	36 (7.1%)	58.1%	26 (7.3%)	41.9%	
>$0 – $100	561 (64.7%)	342 (67.1%)	61.0%	219 (61.3%)	39.0%	
>$100 – $200	110 (12.7%)	55 (10.8%)	50.0%	55 (15.4%)	50.0%	
>$200 – $300	43 (5.0%)	22 (4.3%)	51.2%	21 (5.9%)	48.8%	
>$300 – $400	17 (2.0%)	6 (1.2%)	35.3%	11 (3.1%)	64.7%	
>$400	74 (8.5%)	49 (9.6%)	66.2%	25 (7.0%)	33.8%	
Other out-of-pocket costs, annual total, mean±SD [median][e]	1,799.80± 1,756.32 [1,255.29]	1,848.22± 1,892.38 [1,240.04]		1,730.62± 1,541.22 [1,338.48]		0.98
Other out-of-pocket costs group, n						0.56
$0–$1,000	353 (40.7%)	213 (41.8%)	60.3%	140 (39.2%)	39.7%	
>$1,000–$2,000	227 (26.2%)	128 (25.1%)	56.4%	99 (27.7%)	43.6%	
>$2,000–$3,000	135 (15.6%)	75 (14.7%)	55.6%	60 (16.8%)	44.4%	
>$3,000	152 (17.5%)	94 (18.4%)	61.8%	58 (16.3%)	38.2%	

[a] Percentages for non-adherent and adherent patients were calculated using the total number of patients in each corresponding line item (for categorical variables) instead of n=867 as the denominator.

[b] Comparing the differences between non-adherent and adherent TKI patients. Continuous variables were compared using the Wilcoxon-Mann-Whitney test. Categorical variables were compared using Pearson's chi-squared test or the Fisher's exact test if one or more cells have an expected frequency of five or less.

[c] Significant at the 5% level.

[d] Comorbidities presented were the 10 most prevalent of the 17 Deyo-Charlson conditions among patients in the study cohort excluding cancer. P-values not presented because data is too sparse.
[e] Other out-of-pocket costs include services for outpatient, inpatient, and medications (non-TKI) during the post-index period for which patients had TKI therapy.
CML indicates chronic myeloid leukemia; TKI, tyrosine kinase inhibitor.

Table 6: Adjusted Risk Ratio (ARR) and Adjusted Risk Difference (ARD) of Adherence to TKI Medication Among Patients Newly Diagnosed With CML (n=867)

Characteristics	ARR[a]	95% CI	ARD[a]	95% CI
Mean out-of-pocket costs for a 30-day supply of TKI medication[b]				
$0	Reference		Reference	
>$0 – $100	1.05	0.79 to 1.40	0.02	-0.10 to 0.14
>$100 – $200[b]	1.46	1.12 to 1.90	0.18	0.04 to 0.32
>$200 – $300	1.33	0.93 to 1.89	0.13	-0.06 to 0.32
>$300 – $400[b]	1.62	1.11 to 2.36	0.25	0.01 to 0.50
>$400	0.99	0.66 to 1.47	-0.01	-0.17 to 0.16
Age at the index date, years[b]				
18 – 39	Reference		Reference	
40 – 49	1.21	0.99 to 1.49	0.08	-0.01 to 0.18
50 – 59[b]	1.61	1.33 to 1.96	0.21	0.12 to 0.29
60 – 64[b]	1.60	1.32 to 1.94	0.23	0.12 to 0.33
Male versus female	1.12	0.96 to 1.31	0.05	-0.02 to 0.11
Subscriber (yes versus no)	1.12	0.95 to 1.32	0.05	-0.02 to 0.11
Health plan type				
Group: Comprehensive / Preferred provider organization / Point-of-service / Exclusive provider organization	Reference		Reference	
Consumer-driven health plan / high deductible health plan	1.01	0.77 to 1.34	0.01	-0.11 to 0.12
Health maintenance organization	0.90	0.70 to 1.16	-0.04	-0.14 to 0.06

Characteristics	ARR[a]	95% CI	ARD[a]	95% CI
Missing / Unknown	0.73	0.44 to 1.23	-0.11	-0.27 to 0.05
Region of residence[b]				
South	Reference		Reference	
Northeast	1.18	0.97 to 1.43	0.07	-0.02 to 0.16
North Central[b]	1.25	1.04 to 1.50	0.10	0.01 to 0.18
West[b]	1.33	1.10 to 1.61	0.13	0.04 to 0.22
Unknown	0.81	0.41 to 1.58	-0.08	-0.30 to 0.14
Index year				
2011	Reference		Reference	
2012	0.97	0.78 to 1.19	-0.01	-0.10 to 0.07
2013	1.14	0.94 to 1.38	0.06	-0.03 to 0.14
2014	1.11	0.90 to 1.37	0.04	-0.05 to 0.14
Time to drug index date from diagnosis date, months[b]				
0 – 3	Reference		Reference	
4 – 6[b]	0.61	0.45 to 0.83	-0.17	-0.26 to -0.08
7 – 9[b]	0.47	0.22 to 1.04	-0.22	-0.38 to -0.06
10 – 12[b]	0.48	0.25 to 0.94	-0.22	-0.35 to -0.08
Index treatment				
Imatinib	Reference		Reference	
Dasatinib[b]	1.25	1.06 to 1.48	0.10	0.02 to 0.17
Nilotinib[b]	1.20	1.00 to 1.45	0.08	-0.00 to 0.16
Bosutinib	1.55	0.68 to 3.53	0.23	-0.30 to 0.75
Ponatinib	1.61	0.44 to 5.86	0.25	-0.60 to 1.11

Characteristics	ARR[a]	95% CI	ARD[a]	95% CI
Chronic phase CML (yes versus no)[b]	1.49	1.04 to 2.13	0.14	0.03 to 0.24
Any TKI dose decrease (yes versus no)[b]	0.75	0.59 to 0.95	-0.11	-0.19 to -0.03
Darkow CML Complexity Index				
Usual	Reference		Reference	
Moderate	1.13	0.95 to 1.35	0.05	-0.02 to 0.13
High[b]	1.22	1.00 to 1.48	0.09	-0.00 to 0.18
Deyo-Charlson comorbidity index[b,c]	0.93	0.89 to 0.99	-0.03	-0.06 -to 0.00
Concomitant medications / Number of unique drug classes[c]	1.02	1.00 to 1.05	0.01	-0.00 to 0.02
Mean other out-of-pocket costs, annual total[d]				
$0 – $1,000	Reference		Reference	
>$1,000 – $2,000	0.98	0.80 to 1.19	-0.01	-0.09 to 0.07
>$2,000 – $3,000	0.94	0.74 to 1.20	-0.02	-0.12 to 0.07
>$3,000	0.80	0.62 to 1.03	-0.08	-0.18 to 0.01

[a] ARR and ARD were determined using a multivariate logistic regression model with robust standard error estimates.
[b] Significant at the 5% level.
[c] Treated as continuous.
[d] Other out-of-pocket costs include services for outpatient, inpatient, and medications (non-TKI) during the post-index period for which patients had TKI therapy.
ARD indicates adjusted risk difference; ARR, adjusted risk ratio; CI, confidence interval; CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor.

Table 7: Comparison of Healthcare Utilization Between Adherent and Non-Adherent TKI Patients

	Average Annual Utilization (mean±SD)		Unadjusted		Adjusted	
	Adherent Patients (n = 357)	Non-Adherent Patients (n = 510)	IRR[a]	p-value	IRR[a]	p-value
Outpatient physician visits	16.04±9.00	15.25±12.26	1.05	0.27	0.99	0.89
Emergency room (ER) visits	0.52±1.59	0.63±1.79	0.82	0.34	0.85	0.37
All-cause hospitalizations	0.06±0.29	0.25±0.95	0.25	<0.001[b]	0.32	<0.001[b]
CML-specific hospitalizations	0.03±0.19	0.15±0.72	0.20	<0.001[b]	0.30	<0.01[b]
Number of prescriptions (all drugs)	38.39±27.23	29.27±27.52	1.31	<0.001[b]	1.27	<0.001[b]

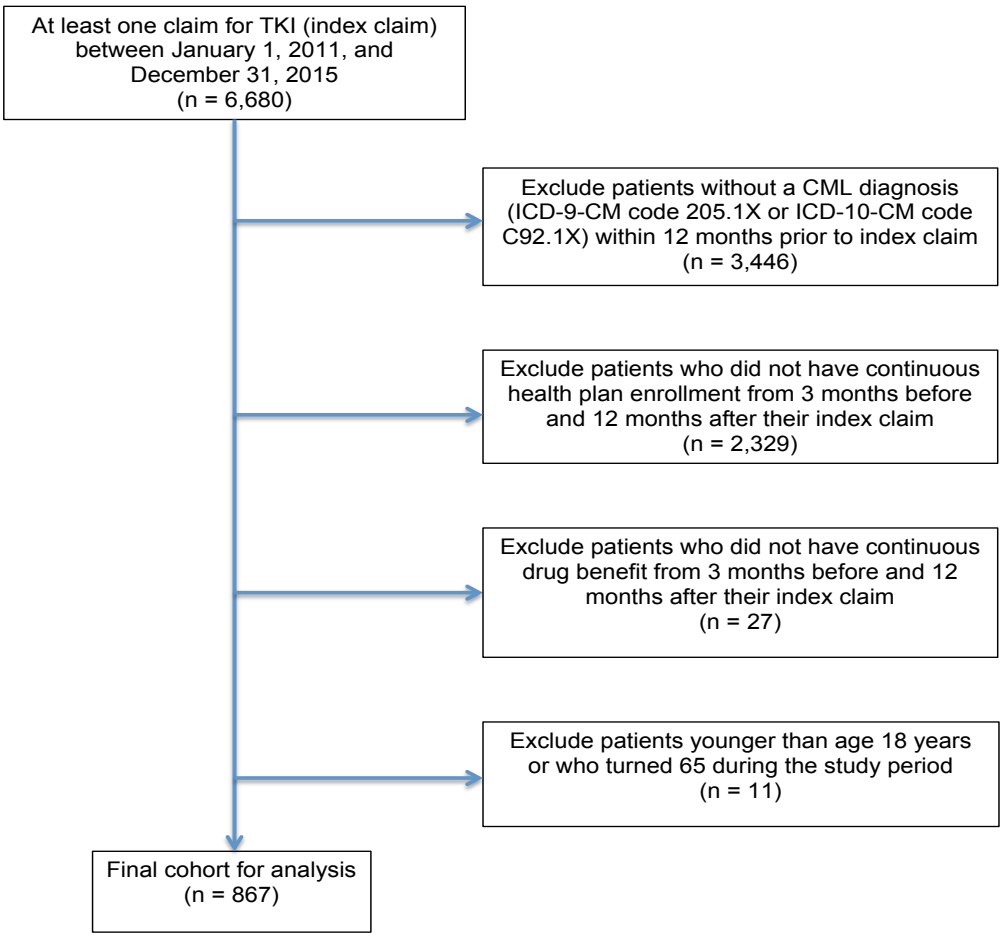
[a] An IRR<1 indicates that adherent patients had lower incidence of incurring medical services compared to non-adherent patients. IRR were estimated using multivariate negative binomial regressions.
[b] Significant at the 5% level.
CML indicates chronic myeloid leukemia; IRR, incidence rate ratio; TKI, tyrosine kinase inhibitor.

Table 8: Comparison of Healthcare Costs Between Adherent and Non-Adherent TKI Patients

	Average Annual Costs (mean±SD)		Unadjusted		Adjusted	
	Adherent Patients (n = 357) [A]	Non-Adherent Patients (n = 510) [B]	Cost Difference[a] [A] – [B]	p-value	Cost Difference[a] (beta coefficient)	p-value
Medical costs	13,015.20±21,034.70	26,966.60±80,379.80	-13,951.40	<0.001[b]	-10,984.74 (-.42)	<0.001[b]
TKI pharmacy costs	108,068.00±26,991.10	74,044.50±38,453.70	34,023.50	<0.001[b]	29,060.22 (.32)	<0.001[b]
Non-TKI pharmacy costs	1,950.16±3,541.10	2,875.54±7,269.88	-925.38	<0.01[b]	-1,641.29 (-.36)	<0.01[b]
Total all-cause healthcare costs	123,033.00±35,576.90	103,887.00±89,574.10	19,146.00	<0.001[b]	19,221.90 (.17)	<0.001[b]

[a] Cost differences <0 indicate that non-adherent patients incurred higher healthcare costs. Cost differences were estimated using multivariate generalized linear models with a gamma distribution and a log link.
[b] Significant at the 5% level.
TKI indicates tyrosine kinase inhibitor.

Figure 3: Study Cohort Selection and Subject Exclusion



CONCLUSION

Patients initiating anticancer drugs face high out-of-pocket costs because prescription drug plans in the United States tend to have cost-sharing mechanisms to control the high costs of these medications. Despite the high costs of TKIs, their optimal use has generated substantial health improvements for CML patients that can reduce the economic burden of CML for insurers through decreased healthcare utilization. We used commercial insurance claims data to show that high costs of TKIs in patients newly diagnosed with CML may be associated with non-adherence. Patients with early initiation of TKI and better adherence had lower risk of adverse events such as hospitalizations, resulting in potential medical service cost savings. Our research studied the association among drug out-of-pocket costs, initiation or adherence, and healthcare utilization or costs within a single study, which is a more comprehensive approach than those found in literature. We measured actual healthcare utilization and costs to determine the effects of initiation or adherence on utilization patterns and direct healthcare costs. Our study documented how TKI initiation delays or non-adherence in CML treatment impacts healthcare utilization and overall healthcare costs. Limitations common to studies using administrative claims data apply in our study, such as potential unobserved confounding, claims coding errors, and missing data. Our use of insurance claims data included information on filled prescriptions only. This prevents us from distinguishing between patients who did not receive a prescription, and patients who received a prescription

but did not fill it. We also assume that patients are taking medications as consistently as they fill their prescriptions. Claims data also do not provide information on the reasons for patients to stop their medications, or any supplemental cost-sharing help patient could have received from patient assistance programs. Future research should focus on assessing barriers to timely access to healthcare for early diagnosis of CML and optimal TKI adherence to advance the understanding of and eliminate health disparities in cancer.

REFERENCES

1. Kochanek KD, Murphy SL, Xu J, Tejada-Vera B. Deaths: Final data for 2014. *Natl Vital Stat Rep*. 2016;65(4):1-122. https://www.cdc.gov/nchs/data/nvsr/nvsr65/nvsr65_04.pdf. Accessed July 5, 2018.

2. American Cancer Society. Cancer facts & figures 2015. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2015/cancer-facts-and-figures-2015.pdf. Updated 2015. Accessed August 3, 2018.

3. American Cancer Society. Cancer facts & figures 2017. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf. Updated 2017. Accessed July 5, 2018.

4. American Cancer Society. Cancer facts & figures 2010. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2010/cancer-facts-and-figures-2010.pdf. Updated 2010. Accessed July 5, 2018.

5. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the united states: 2010-2020. *J Natl Cancer Inst*. 2011;103(2):117-

128. https://www-ncbi-nlm-nih-gov.utsph.idm.oclc.org/pmc/articles/PMC3107566/. Accessed August 3, 2018.

6. National Cancer Institute. Targeted cancer therapies. https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet. Updated 2018. Accessed July 5, 2018.

7. American Society of Clinical Oncology. The state of cancer care in america, 2015: A report by the american society of clinical oncology. *J Oncol Pract*. 2015;11(2):79-113. http://ascopubs.org/doi/pdf/10.1200/JOP.2015.003772. Accessed July 5, 2018.

8. Johnson K, Blansett L, Mawrie R, Di Biase S. Innovation in cancer care and implications for health systems: Global oncology trend report. *IMS Institute for Healthcare Informatics*. 2014;May. http://allianceforpatientaccess.org/wp-content/uploads/2014/06/IMSH_Oncology_Trend_Report.pdf. Accessed July 5, 2018.

9. American Cancer Society. Targeted therapies for chronic myeloid leukemia. https://www.cancer.org/cancer/chronic-myeloid-leukemia/treating/targeted-therapies.html. Updated 2018. Accessed August 3, 2018.

10. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Chronic myeloid leukemia.

https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. Updated 2018. Accessed June 23, 2018.

11. National Cancer Institute SEER Program. Cancer stat facts: Leukemia - chronic myeloid leukemia (CML). https://seer.cancer.gov/statfacts/html/cmyl.html. Updated 2018. Accessed August 4, 2018.

12. Sawyers CL. Chronic myeloid leukemia. *N Engl J Med*. 1999;340(17):1330-1340. https://www-nejm-org.utsph.idm.oclc.org/doi/full/10.1056/NEJM199904293401706. Accessed June 23, 2018.

13. Cuellar S, Vozniak M, Rhodes J, Forcello N, Olszta D. BCR-ABL1 tyrosine kinase inhibitors for the treatment of chronic myeloid leukemia. *J Oncol Pharm Pract*. 2017. http://journals.sagepub.com.utsph.idm.oclc.org/doi/abs/10.1177/1078155217710553. Accessed June 23, 2018.

14. Mathisen MS, Kantarjian HM, Cortes J, Jabbour EJ. Practical issues surrounding the explosion of tyrosine kinase inhibitors for the management of chronic myeloid leukemia. *Blood Rev*. 2014;28(5):179-187. https://www.bloodreviews.com/article/S0268-960X(14)00042-3/fulltext. Accessed June 23, 2018.

15. CenterWatch. FDA approved drugs for oncology. http://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/12/oncology. Updated 2018. Accessed June 26, 2018.

16. Experts in Chronic Myeloid Leukemia. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: From the perspective of a large group of CML experts. *Blood*. 2013;121(22):4439-4442. http://www.bloodjournal.org/content/121/22/4439.full. Accessed June 23, 2018.

17. National Comprehensive Cancer Network. NCCN guidelines for patients®: Chronic myeloid leukemia. https://www.nccn.org/patients/guidelines/cml/. Updated 2018. Accessed August 4, 2018.

18. National Cancer Institute. Chronic myelogenous leukemia treatment - health professional version. https://www.cancer.gov/types/leukemia/hp/cml-treatment-pdq. Updated 2018. Accessed June 23, 2018.

19. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67:7-30. https://onlinelibrary.wiley.com/doi/10.3322/caac.21387. Accessed June 23, 2018.

20. Noens L, van Lierde MA, De Bock R, et al. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: The ADAGIO study. *Blood*. 2009;113(22):5401-5411.

http://www.bloodjournal.org/content/113/22/5401.short?sso-checked=true. Accessed June 23, 2018.

21. Marin D, Bazeos A, Mahon F, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *J Clin Oncol*. 2010;28(14):2381-2388. http://ascopubs.org/doi/full/10.1200/JCO.2009.26.3087. Accessed June 23, 2018.

22. Ganesan P, Sagar TG, Dubashi B, et al. Nonadherence to imatinib adversely affects event free survival in chronic phase chronic myeloid leukemia. *Am J Hematol*. 2011;86(6):471-474. https://onlinelibrary-wiley-com.utsph.idm.oclc.org/doi/full/10.1002/ajh.22019. Accessed August 4, 2018.

23. Ibrahim AR, Eliasson L, Apperley JF, et al. Poor adherence is the main reason for loss of CCyR and imatinib failure for chronic myeloid leukemia patients on long-term therapy. *Blood*. 2011;117(14):3733-3736. http://www.bloodjournal.org/content/117/14/3733. Accessed June 23, 2018.

24. Di Bella NJ, Bhowmik D, Bhor M, et al. The effectiveness of tyrosine kinase inhibitors and molecular monitoring patterns in newly diagnosed patients with chronic myeloid leukemia in the community setting. *Clin Lymphoma Myeloma Leuk*. 2015;15(10):599-605. https://www-sciencedirect-com.utsph.idm.oclc.org/science/article/pii/S2152265015003833. Accessed August 4, 2018.

25. Kekale M, Talvensaari K, Koskenvesa P, Porkka K, Airaksinen M. Chronic myeloid leukemia patients' adherence to peroral tyrosine kinase inhibitors compared with adherence as estimated by their physicians. *Patient Prefer Adherence*. 2014;8:1619-1627. https://www-ncbi-nlm-nih-gov.utsph.idm.oclc.org/pmc/articles/PMC4246993/. Accessed August 4, 2018.

26. Santoleri F, Lasala R, Ranucci E, et al. Medication adherence to tyrosine kinase inhibitors: 2-year analysis of medication adherence to imatinib treatment for chronic myeloid leukemia and correlation with the depth of molecular response. *Acta Haematol*. 2016;136(1):45-51.

27. Efficace F, Rosti G, Cottone F, et al. Profiling chronic myeloid leukemia patients reporting intentional and unintentional non-adherence to lifelong therapy with tyrosine kinase inhibitors. *Leuk Res*. 2014;38(3):294-298. https://www-sciencedirect-com.utsph.idm.oclc.org/science/article/pii/S0145212613002300. Accessed July 6, 2018.

28. Dusetzina SB, Winn AN, Abel GA, Huskamp HA, Keating NL. Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. *J Clin Oncol*. 2013;32(4):306-311. http://ascopubs.org/doi/full/10.1200/JCO.2013.52.9123. Accessed June 26, 2018.

29. Perry AM, Brunner AM, Zou T, et al. Association between insurance status at diagnosis and overall survival in chronic myeloid leukemia: A population-based study. *Cancer*. 2017;123(13):2561-2569. https://onlinelibrary-wiley-com.utsph.idm.oclc.org/doi/pdf/10.1002/cncr.30639. Accessed August 4, 2018.

30. Briesacher BA, Gurwitz JH, Soumerai SB. Patients at-risk for cost-related medication nonadherence: A review of the literature. *J Gen Intern Med*. 2007;22(6):864-871. https://link-springer-com.utsph.idm.oclc.org/article/10.1007/s11606-007-0180-x. Accessed July 5, 2018.

31. Piette JD, Heisler M. Problems due to medication costs among VA and non-VA patients with chronic illnesses. *Am J Manag Care*. 2004;10(11 Pt 2):861-868. https://www.ajmc.com/journals/issue/2004/2004-11-vol10-n11pt2/nov04-1951p861-868?p=1. Accessed August 4, 2018.

32. Huntington SF, Davidoff AJ. High-cost, high-value oral specialty drugs: More evidence on the impact of cost sharing in medicare part D. *J Clin Oncol*. 2016;34(36 (Dec 20)):4307-4309. http://ascopubs.org/doi/full/10.1200/JCO.2016.70.2738. Accessed August 4, 2018.

33. Streeter SB, Schwartzberg L, Husain N, Johnsrud M. Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions. *J Oncol Pract*. 2011;7(3 SUPPL.):46s-51s.

http://ascopubs.org/doi/pdfdirect/10.1200/jop.2011.000316. Accessed August 4, 2018.

34. Eaddy MT, Cook CL, O'Day K, Burch SP, Cantrell CR. How patient cost-sharing trends affect adherence and outcomes: A literature review. *P T*. 2012;37(1):45-55. https://www-ncbi-nlm-nih-gov.utsph.idm.oclc.org/pmc/articles/PMC3278192/. Accessed August 4, 2018.

35. Stern D, Reissman D. Specialty pharmacy cost management strategies of private health care payers. *J Manag Care Pharm*. 2006;12(9):736-744. https://www.jmcp.org/doi/pdf/10.18553/jmcp.2006.12.9.736. Accessed August 4, 2018.

36. Raborn ML, Pelletier EM, Smith DB, Reyes CM. Patient out-of-pocket payments for oral oncolytics: Results from a 2009 US claims data analysis. *J Oncol Pract*. 2012;8(3 Suppl):9s-15s. http://ascopubs.org/doi/pdfdirect/10.1200/JOP.2011.000516. Accessed August 4, 2018.

37. Goldman DP, Joyce GF, Lawless G, Crown WH, Willey V. Benefit design and specialty drug use. *Health Aff*. 2006;25(5):1319-1331. https://www-healthaffairs-org.utsph.idm.oclc.org/doi/pdf/10.1377/hlthaff.25.5.1319. Accessed August 4, 2018.

38. Goldman DP, Joyce GF, Zheng Y. Prescription drug cost sharing: Associations with medication and medical utilization and spending and health. *JAMA*. 2007;298(1):61-69. https://www.researchgate.net/publication/6229235_Prescription_Drug_Cost_Sharing_Associations_With_Medication_and_Medical_Utilization_and_Spending_and_Health. Accessed July 5, 2018.

39. Majumdar SR. Cost sharing and the initiation of drug therapy for the chronically ill—invited commentary. *Arch Intern Med*. 2009;169(8):748-749. https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/224582. Accessed August 4, 2018.

40. Kantarjian H, Ho V. High cancer drug prices: The harm to americans and proposed solutions. https://scholarship.rice.edu/bitstream/handle/1911/93932/BI-Brief-2016-Rec_Kantarjian.pdf?sequence=1. Updated 2016. Accessed August 4, 2018, 2018.

41. Sedjo RL, Devine S. Predictors of non-adherence to aromatase inhibitors among commercially insured women with breast cancer. *Breast Cancer Res Treat*. 2011;125(1):191-200. https://link-springer-com.utsph.idm.oclc.org/article/10.1007/s10549-010-0952-6. Accessed August 4, 2018.

42. Kirk MC, Hudis CA. Insight into barriers against optimal adherence to oral hormonal therapy in women with breast cancer. *Clin Breast Cancer*. 2008;8(2):155-161. https://www.clinical-breast-cancer.com/article/S1526-8209(11)70502-X/abstract. Accessed August 4, 2018.

43. Neugut AI, Subar M, Wilde ET, et al. Association between prescription co-payment amount and compliance with adjuvant hormonal therapy in women with early-stage breast cancer. *J Clin Oncol*. 2011;29(18):2534-2542. https://www-ncbi-nlm-nih-gov.utsph.idm.oclc.org/pmc/articles/PMC3138633/. Accessed August 4, 2018.

44. Heisler M, Wagner TH, Piette JD. Patient strategies to cope with high prescription medication costs: Who is cutting back on necessities, increasing debt, or underusing medications? *J Behav Med*. 2005;28(1):43-51. https://link-springer-com.utsph.idm.oclc.org/content/pdf/10.1007/s10865-005-2562-z.pdf. Accessed August 4, 2018.

45. Guérin A, Chen L, Dea K, Wu EQ, Goldberg SL. Association between regular molecular monitoring and tyrosine kinase inhibitor therapy adherence in chronic myelogenous leukemia in the chronic phase. *Curr Med Res Opin*. 2014;30(7):1345-1352.

46. Noens L, Hensen M, Kucmin-Bemelmans I, Lofgren C, Gilloteau I, Vrijens B. Measurement of adherence to BCR-ABL inhibitor therapy in chronic myeloid

leukemia: Current situation and future challenges. *Haematologica*. 2014;99(3):437-447. http://www.haematologica.org.utsph.idm.oclc.org/content/99/3/437.short. Accessed July 6, 2018.

47. Darkow T, Maclean JR, Joyce GF, Goldman D, Lakdawalla DN. Coverage and use of cancer therapies in the treatment of chronic myeloid leukemia. *Am J Manag Care*. 2012;18:S272-S278. https://www.ajmc.com/journals/supplement/2012/a386_12nov_oncology/a386_12nov_onclogy_darkow_s272to78?p=1. Accessed July 6, 2018.

48. Darkow T, Henk HJ, Thomas SK, et al. Treatment interruptions and non-adherence with imatinib and associated healthcare costs. *Pharmacoeconomics*. 2007;25(6):481-496. https://link-springer-com.utsph.idm.oclc.org/article/10.2165/00019053-200725060-00004. Accessed June 23, 2018.

49. Kropf P, Barnes G, Tang B, Pathak A, Issa JJ. Healthcare utilization and costs associated with tyrosine kinase inhibitor switching in patients with chronic myeloid leukemia. *Leuk Lymphoma*. 2016;57(4):935-941. https://www-tandfonline-com.utsph.idm.oclc.org/doi/abs/10.3109/10428194.2015.1088654. Accessed July 6, 2018.

50. Wu EQ, Johnson S, Beaulieu N, et al. Healthcare resource utilization and costs associated with non-adherence to imatinib treatment in chronic myeloid leukemia

patients. *Curr Med Res Opin*. 2010;26(1):61-69. https://www-tandfonline-com.utsph.idm.oclc.org/doi/abs/10.1185/03007990903396469. Accessed June 23, 2018.

51. Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012;73(5):691-705. https://bpspubs-onlinelibrary-wiley-com.utsph.idm.oclc.org/doi/full/10.1111/j.1365-2125.2012.04167.x. Accessed August 4, 2018.

52. Barillet M, Prevost V, Joly F, Clarisse B. Oral antineoplastic agents: How do we care about adherence? *Br J Clin Pharmacol*. 2015;80(6):1289-1302. https://bpspubs-onlinelibrary-wiley-com.utsph.idm.oclc.org/doi/pdf/10.1111/bcp.12734. Accessed August 4, 2018.

53. Winn AN, Keating NL, Dusetzina SB. Factors associated with tyrosine kinase inhibitor initiation and adherence among medicare beneficiaries with chronic myeloid leukemia. *J Clin Oncol*. 2016;34(36):4323-4328. https://www-ncbi-nlm-nih-gov.utsph.idm.oclc.org/pmc/articles/PMC5455309/. Accessed June 25, 2018.

54. Doshi JA, Li P, Huo H, et al. High cost sharing and specialty drug initiation under medicare part D: A case study in patients with newly diagnosed chronic myeloid leukemia. *Am J Manag Care*. 2016;22(4 Suppl):S78-S86. https://www.ajmc.com/journals/supplement/2016/improving-patient-access-to-critical-therapies-in-the-age-of-cost-sharing/high-cost-sharing-and-specialty-drug-

initiation-under-medicare-part-d-a-case-study-in-patients-with-newly-diagnosed-cml. Accessed June 23, 2018.

55. Andersen R, Newman JF. Societal and individual determinants of medical care utilization in the united states. *Milbank Q*. 2005;83(4):Online-only. https://onlinelibrary-wiley-com.utsph.idm.oclc.org/doi/full/10.1111/j.1468-0009.2005.00428.x. Accessed August 4, 2018.

56. Piette JD, Heisler M, Horne R, Alexander GC. A conceptually based approach to understanding chronically ill patients' responses to medication cost pressures. *Soc Sci Med*. 2006;62(4):846-857. https://www-sciencedirect-com.utsph.idm.oclc.org/science/article/pii/S0277953605003606. Accessed August 4, 2018.

57. Jabbour E, Saglio G, Radich J, Kantarjian H. Adherence to BCR-ABL inhibitors: Issues for CML therapy. *Clin Lymphoma Myeloma Leuk*. 2012;12(4):223-229. https://www.clinical-lymphoma-myeloma-leukemia.com/article/S2152-2650(12)00056-0/fulltext. Accessed June 23, 2018.

58. Feng W, Henk H, Thomas S, et al. Compliance and persistency with imatinib. *J Clin Oncol*. 2006;24(18_suppl):6038-6038. http://ascopubs.org/doi/abs/10.1200/jco.2006.24.18_suppl.6038. Accessed August 4, 2018.

59. StCharles M, Bollu VK, Hornyak E, Coombs J, Blanchette CM, DeAngelo DJ. Predictors of treatment non-adherence in patients treated with imatinib mesylate for chronic myeloid leukemia. *Blood*. 2009;114(22):2209. http://www.bloodjournal.org/content/114/22/2209. Accessed June 23, 2018.

60. Henk HJ, Woloj M, Shapiro M, Whiteley J. Real-world analysis of tyrosine kinase inhibitor treatment patterns among patients with chronic myeloid leukemia in the united states. *Clin Ther*. 2015;37(1):124-133. https://www.clinicaltherapeutics.com/article/S0149-2918(14)00692-4/fulltext. Accessed June 23, 2018.

61. Hall AE, Paul C, Bryant J, et al. To adhere or not to adhere: Rates and reasons of medication adherence in hematological cancer patients. *Crit Rev Oncol*. 2016;97:247-262. https://www.croh-online.com/article/S1040-8428(15)30040-8/fulltext. Accessed June 23, 2018.

62. Larizza MA, Dooley MJ, Stewart K, Kong D. Factors influencing adherence to molecular therapies in Haematology-Oncology outpatients. *J Pharm Pract Res*. 2006;36(2):115-118. https://onlinelibrary-wiley-com.utsph.idm.oclc.org/doi/abs/10.1002/j.2055-2335.2006.tb00584.x. Accessed June 23, 2018.

63. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619. https://www-sciencedirect-com.utsph.idm.oclc.org/science/article/pii/0895435692901338. Accessed June 23, 2018.

64. Ward MA, Fang G, Richards KL, et al. Comparative evaluation of patients newly initiating first-generation versus second-generation tyrosine kinase inhibitors for chronic myeloid leukemia and medication adherence, health services utilization, and healthcare costs. *Curr Med Res Opin*. 2015;31(2):289-297. https://www-tandfonline-com.utsph.idm.oclc.org/doi/abs/10.1185/03007995.2014.991440. Accessed June 25, 2018.

65. Bazeos A, Khorashad J, Mahon F, et al. Long term adherence to imatinib therapy is the critical factor for achieving molecular responses in chronic myeloid leukemia patients. *ASH Annual Meeting*. 2009;3290(Abstract). http://www.bloodjournal.org/content/114/22/3290?sso-checked=true. Accessed August 4, 2018.

66. Eliasson L, Clifford S, Barber N, Marin D. Exploring chronic myeloid leukemia patients' reasons for not adhering to the oral anticancer drug imatinib as prescribed. *Leuk Res*. 2011;35(5):626-630. https://www-sciencedirect-

com.utsph.idm.oclc.org/science/article/pii/S0145212610005102. Accessed July 6, 2018.

67. Truven Health MarketScan® Research Databases. Commercial claims and encounters: Data year 2015 edition. *Truven Health Analytics*. 2016.

68. Kaiser Family Foundation. Health insurance coverage of the total population - timeframe: 2015. http://www.kff.org/other/state-indicator/total-population/?dataView=0&currentTimeframe=0&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D. Updated 2018. Accessed August 4, 2018.