Association of Generic Imatinib Availability and Pricing With Trends in Tyrosine Kinase Inhibitor Use in Patients With Chronic Myelogenous Leukemia

The increasing price of new cancer therapies over the past 3 decades has contributed considerably to increasing health care expenditures. The life expectancy of patients with chronic myelogenous leukemia (CML) treated with imatinib now approaches that of the general population, increasing the prevalence of survivors with CML receiving treatment.1 Beginning in 2006, a series of second- and third-generation tyrosine kinase inhibitors (TKIs) have been approved and gained widespread use based on early results demonstrating deeper molecular responses.2,3 However, subsequent studies have provided no evidence that later-generation TKIs provide superior progression free or overall survival compared with imatinib.4-6 Although a generic imatinib was approved in 2016, high initial prices of brand name and generic imatinib and next-generation TKIs have continued to increase, averaging 10% to 20% annually, contributing to financial hardship and possibly poor compliance with effective therapy (https://ascopubs.org/doi/10.1200/JOP.2016.019737). In this article, we provide contemporary data to identify trends in TKI use in patients with CML and the association those treatment choices have with health care costs.

Methods | Health plan enrollees initiating treatment with a TKI (eg, imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) from January 1, 2010, to December 31, 2019, were identified in the OptumLabs Data Warehouse. The database contains deidentified medical and pharmacy claims information on commercial and Medicare Advantage enrollees. Because this study involved analysis of preexisting, deidentified data, it was exempt from institutional review board approval and informed consent according to the US Health Insurance Portability and Accountability Act. Eligible patients had received a diagnosis of CML (International Classification of Diseases, Ninth Revision [ICD-9] code 205.1x or International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10] code C92.1x) and enrolled at least 6 months before their first TKI prescription fill. Patients who underwent stem cell transplant before starting a TKI were excluded. We identified choice of first-line TKI, switching to another TKI, and health care costs in the first year of treatment (the latter 2 requiring 12 months of enrollment following TKI initiation). First-year TKI costs are reported as cost per TKI treatment day ([health plan + patient paid amount]/total days' supply). All analyses were conducted using Stata, version 14.2 (StataCorp).

Results | The proportion of patients beginning to take a second- or third-generation drug (eg, dasatinib, nilotinib, bosutinib, or ponatinib) increased from 28 of 148 (19%) in 2010 to 146 of 263 (56%) in 2019 (Figure, A). Approximately 1 in 4 switched from their initial TKI within the first year of treatment (Table). By the end of the first year of treatment, second- or third-generation TKI use rose from 37 of 108 (34%) to 137 of 213 (64%) from 2010 to 2018 (Figure, B).

Tyrosine kinase inhibitor costs are the largest driver of health care expenditures in patients with CML, representing 66% of first-year spending for Medicare Advantage members in 2018 and 65% for commercial enrollees (https://ascopubs.org/doi/full/10.1200/OP.20.00143). Tyrosine kinase inhibitor costs per day have increased from $243 for those undergoing treatment in 2010 to $354 in 2018 (Table).
Table. Trend in TKI Switching and Costs in First Year of Treatment*

<table>
<thead>
<tr>
<th>Year of treatment initiation</th>
<th>No.</th>
<th>Switching, No. (%)</th>
<th>Days' supply, median (IQR)</th>
<th>TKI cost per treated day, mean (95% CI), $a,b,c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HPP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OOP</td>
</tr>
<tr>
<td>2010</td>
<td>108</td>
<td>17 (16)</td>
<td>346 (268-365)</td>
<td>243 (228-259)</td>
</tr>
<tr>
<td>2011</td>
<td>146</td>
<td>26 (18)</td>
<td>352 (300-365)</td>
<td>275 (263-286)</td>
</tr>
<tr>
<td>2012</td>
<td>161</td>
<td>36 (23)</td>
<td>336 (264-360)</td>
<td>283 (272-294)</td>
</tr>
<tr>
<td>2013</td>
<td>131</td>
<td>26 (20)</td>
<td>350 (270-365)</td>
<td>305 (294-317)</td>
</tr>
<tr>
<td>2014</td>
<td>144</td>
<td>27 (20)</td>
<td>353 (307-365)</td>
<td>350 (338-362)</td>
</tr>
<tr>
<td>2015</td>
<td>147</td>
<td>31 (22)</td>
<td>331 (255-363)</td>
<td>367 (355-378)</td>
</tr>
<tr>
<td>2016</td>
<td>173</td>
<td>39 (24)</td>
<td>336 (268-364)</td>
<td>353 (338-369)</td>
</tr>
<tr>
<td>2017</td>
<td>202</td>
<td>38 (20)</td>
<td>344 (280-365)</td>
<td>343 (323-364)</td>
</tr>
<tr>
<td>2018</td>
<td>213</td>
<td>45 (23)</td>
<td>321 (240-352)</td>
<td>354 (325-383)</td>
</tr>
</tbody>
</table>

Abbreviations: CPI, consumer price index; HPP, health plan paid amount; IQR, interquartile range; OOP, patient out-of-pocket responsibility; TKI, tyrosine kinase inhibitor.

a Patients are required to have 1 year of continuous enrollment following TKI treatment initiation.

b Because of the availability of health plan cost information for the entire year following treatment initiation, the 2018 sample size was 128.

c Calculated as health plan + patient paid amount for TKI divided by total days’ supply in the first year. Costs are converted to 2018 dollars using the medical component of the CPI.

Discussion | Despite the lack of evidence for an overall survival difference between first- or second-generation TKIs, most patients with CML are now prescribed a second-generation TKI in the US. 2, 4-6 Despite a National Average Drug Acquisition Cost price for generic imatinib as low as $20 per 400-mg tablet in 2018, the average TKI costs per day exceeded $350, largely driven by the decision to treat patients with CML with more costly second-line TKIs (https://ascopubs.org/doi/full/10.1200/JCO.2015.64.8899). High costs may result in treatment delays, poor compliance, or early termination of effective therapy, leading to poorer outcomes for individuals with a treatable and potentially curable malignancy. While the US patent on dasatinib expires in October 2025, the association with generic TKIs remaining on patent beyond 2030. Our results are limited to data from managed care enrollees, which may not reflect the experience of other populations (eg, those without insurance or those receiving Medicaid).

In conclusion, generic price competition alone may be insufficient to reduce the price of cancer drugs in the US. Another potential driver is delays in some pharmacies passing on lower acquisition prices. Policies that address rising cancer drug prices and overall health care expenditures must be of the highest priority for clinicians, payers, patient advocates, and policy makers moving forward.

Gary H. Lyman, MD, MPH
Henry J. Henk, PhD

Author Contributions: Dr Henk had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: All authors. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: All authors. Obtained funding: All authors. Administrative, technical, or material support: Henk. Supervision: Henk.

Conflict of Interest Disclosures: None reported.

Funding: This research was supported by a Stand Up to Cancer award (SU2C-AACR-SUPHOPD1). SU2C is a program of the Entertainment Industry Foundation; research grants are administered by the American Association for Cancer Research, a scientific partner of SU2C.

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank Eric J. Chow, MD, Fred Hutchinson Cancer Research Center, for data acquisition and Pamela Morin, MBA, OptumLabs, for analytic dataset construction. No individuals received compensation for their contributions.

Early Trastuzumab Interruption and Recurrence-Free Survival in ERBB2-Positive Breast Cancer

Human epidermal growth factor receptor 2 (ERBB2)-targeted therapies such as trastuzumab improve disease-free and overall survival for patients with ERBB2-positive breast cancer (BCA). Cardiotoxic effects, characterized by reduced left ventricular ejection fraction (LVEF) or clinical heart failure (HF), are an important treatment-limiting adverse effect of ERBB2-targeted therapy and the most common indication for early trastuzumab interruption. Findings from the PHARE and PERSEPHONE trials on the noninferiority of 6- vs 12-month durations of trastuzumab are conflicting, thus the clinical significance of early trastuzumab interruption on BCA outcomes remains uncertain. Our primary objective was to evaluate the association of early trastuzumab interruption with BCA outcomes in clinical practice.

Methods | All patients with early-stage ERBB2-positive BCA treated with trastuzumab at Memorial Sloan Kettering Cancer Center (MSKCC) from 2004 to 2013 were identified. The study was approved by the MSKCC institutional review board and a waiver of written informed consent was granted because data were deidentified. Early interruption, defined as a 6-week or longer interval between scheduled trastuzumab doses, was ascertained. Indications for interruption were cardiac (ie, asymptomatic LVEF decline or HF) vs noncardiac. The primary outcome was recurrence-free survival (RFS), defined as time from start of trastuzumab to the date of invasive BCA recurrence or all-cause death. Survival was estimated using the Kaplan-Meier method with a 12-month landmark, given that treatment interruption occurs within this timeframe of initiating trastuzumab and to account for bias from patients with early interruption owing to disease recurrence. Multivariable Cox proportional hazards models evaluated associations between RFS and treatment interruption and treatment interruption by indication (no interruption, cardiac interruption, or noncardiac interruption) or cumulative trastuzumab dose (no interruption, ≤56 mg/kg, or >56 mg/kg), adjusting for age, anthracycline, cancer stage, estrogen/progesterone receptor status, hypertension, and diabetes. A dose cutoff of 56 mg/kg was chosen because this approximates 6 months of trastuzumab treatment. Statistical analyses were performed using STATA statistical software (version 16.1, StataCorp).

Results | Among 1396 trastuzumab-treated patients (median [interquartile range] age, 51 [44-59] years), treatment interruption occurred in 184 (13%)–124 (67%) for cardiotoxic effects (92 with LVEF decline and 32 with HF) and 60 for noncardiac reasons. After median follow-up of 6.0 years, invasive BCA recurrence or death occurred in 44 (24%) of 184 in the interrupted group and 153 (13%) of 1212 in the continuous group (log-rank P < .001) (Figure). Patients with early trastuzumab interruption had a significantly increased hazard of invasive BCA recurrence or death (adjusted hazard ratio [HR], 1.56; 95% CI, 1.10-2.21) (Table). The adjusted HR for RFS was 1.47 (95% CI, 0.98-2.20) in the group with a cardiac interruption and 1.78 (95% CI, 1.03-3.08) in the group with a noncardiac interruption. Sixty (33%) patients in the interrupted group and none in the continuous group received a cumulative trastuzumab dose of 56 mg/kg or less. Trastuzumab interruption with a cumulative trastuzumab dose of 56 mg/kg or less was associated with reduced RFS with an adjusted HR of 1.96 (95% CI, 1.16-3.33).

Discussion | This study demonstrates that patients with early trastuzumab interruption had higher rates of BCA recurrence and death compared with patients receiving uninterrupted treatment. Importantly, RFS was reduced in patients with early treatment interruption who received a cumulative trastuzumab dose of 56 mg/kg or less (equivalent to ≤6 months of trastuzumab), suggesting that the total trastuzumab dose plays an important role in BCA outcomes. The most common cause for early interruption was cardiotoxic effects, accounting for 124 (67%) of 184 cases, highlighting the potential that such interruptions may adversely affect BCA outcomes. Given that most patients in this study were treated with anthracyclines, our findings may not be generalizable to patients receiving nonanthracycline treatment regimens. Recent studies suggest that asymptomatic LVEF declines can safely be treated without interrupting trastuzumab when close cardiac monitoring and appropriate cardiac medications are instituted. Given that current clinical trial data are insufficient to support shortened durations of trastuzumab, ongoing collaboration between cardiologists and oncologists is needed to minimize treatment interruptions and allow patients with asymptomatic LVEF decline to continue receiving ERBB2-targeted therapy.

Robert S. Copeland-Halperin, MD
Mohammed Al-Sadawi, MD
Sujata Patil, PhD
Jennifer E. Liu, MD
Richard M. Steingart, MD
Chau T. Dang, MD
Anthony F. Yu, MD, MS