Coverage and Use of Cancer Therapies in the Treatment of Chronic Myeloid Leukemia

Theodore Darkow, PharmD; J. Ross Maclean, MD; Geoffrey F. Joyce, PhD; Dana Goldman, PhD; and Darius N. Lakdawalla, PhD

Abstract

Objectives: This study was designed to assess the effect of tyrosine kinase inhibitor (TKI) use on non-pharmaceutical medical spending for patients with chronic myeloid leukemia (CML), and estimate the association between cost-sharing and the TKI medication possession ratio (MPR).

Study Design: The retrospective study covered the 13 years from 1997 to 2009.

Methods: Analyses were conducted using a large administrative health insurance claims database covering 45 large employers. From this database, 995 unique patients with CML were identified, with 3,765 patient-years; of these patients, 415 (or 1,689 patient-years) were TKI users. We estimated the association of TKI use with total pharmaceutical spending and total non-pharmaceutical medical spending. In addition, we characterized plan-level cost-sharing rules for TKIs and assessed whether these were associated with the MPR for TKI therapy among CML patients.

Results: TKI users averaged $26,406 in annual non-pharmaceutical medical spending, compared with $38,194 for non-users; this was a difference of approximately 30%, which was statistically significant at the 5% level. The median patient out-of-pocket payment was $25, which increased to $63 at the 75th percentile and to $122 at the 95th percentile. MPRs were 94.8 at the median cost-sharing level and 100.0 at the 75th percentile and higher. There was no statistically significant association between cost-sharing and MPR.

Conclusions: Use of TKIs was associated with a 30% reduction in non-pharmaceutical medical spending for CML patients. This difference is approximately equal to 40% of the incremental pharmaceutical cost associated with using TKI therapy. The net annual cost of TKI therapy is roughly $15,000. An informal calculation suggests that this is well within the range of conventional cost-effectiveness thresholds. On balance, coverage of TKIs is relatively generous, with the vast majority of patients exhibiting high levels of adherence to therapy.

(Am J Manag Care. 2012;18:S272-S278)

For author information and disclosures, see end of text.

Advances in biotechnology have produced many effective new treatments for serious and debilitating diseases. This is evidenced by the growth in use of specialty products and by the number of specialty products in the pipeline, most strikingly in the field of oncology. The number of investigational new drug applications for cancer treatment rose from 925 in 2003 to 1,440 in 2008.[1] In addition, the price of oncologics has been increasing over time: the most expensive chemotherapy agent in the early 1990s was paclitaxel, which sold for $4,000 per year, while today, the cost of bevacizumab is 10 times higher.[2]

As utilization of and spending on cancer medications increase, both public and private insurers have adopted a more aggressive approach to managing reimbursement, distribution, and benefit designs. For example, most Medicare Part D plans place medications costing $600 or more per month (primarily cancer agents) on a special tier with higher cost-sharing requirements.[3] In 2009, 96% of plans had a specialty tier, with virtually every plan imposing coinsurance rates of 25% to 33%.[4]

While lack of insurance is almost certainly a barrier to accessing specialty cancer medications, it is unclear whether demand for these products is affected by the cost-sharing burden imposed on patients by insurance benefit design. The tradeoff between risk-sharing and appropriate incentives raises the issue of how and to what extent payers should cover these products. Benefit-design decisions regarding cancer agents are particularly challenging given the severity of the illnesses they are designed to treat, the diversity of patient responsiveness to therapy, and widespread off-label use within the field of oncology.[5] The principal challenge facing society is balancing the need to ensure access to a wide range of therapeutic alternatives and the need to constrain the rapid growth in healthcare expenditures. In order to do this effectively, more information is needed on clinical efficacy, price sensitivity, and overall value.

In this article, we estimate coverage and demand for a specific class of high-cost cancer therapies; namely, tyrosine kinase inhibitors (TKIs). Imatinib was introduced in 2001 and quickly became the standard of care for patients with newly diagnosed chronic myeloid leukemia (CML).[6] Since then, dasatinib and nilotinib have been introduced and are associated with significantly higher and faster rates of complete cytogenetic response,

and better long-term, progression-free survival versus imatinib.[7] Dasatinib and nilotinib were originally introduced as second-line therapies in 2006 and 2007, respectively; both agents were approved for first-line use in 2010, given their demonstrated superiority to imatinib in this setting.[7,8]

While these medications can dramatically alter the course of disease progression, they can cost $50,000 to $100,000 per year.[9] For this reason, we examined the ways in which these products are covered in employer-sponsored plans, the degree of demand sensitivity to cost-sharing, and the extent to which spending on these products affects use of other healthcare services.

Chronic Myeloid Leukemia and the Role of TKIs

CML is a slowly progressing blood and bone marrow disease that is usually diagnosed during or after middle age, and is rarely diagnosed in children. Prognosis and treatment options depend upon the patient's age, the stage at diagnosis, the load of blasts in the blood (or bone marrow), and the patient's general health.

TKIs work by targeting a specific protein that promotes cancer cell growth.[10] While it is not possible to eliminate all leukemia cells, treatment can help achieve long-term remission of the disease. The prognosis for patients with CML has improved dramatically over the past decade. Prior to the introduction of TKIs, fewer than 20% of patients survived 10 years after diagnosis. First-line treatment with a TKI agent increased 10-year survival rates to 85% or more.[11] Because complete response is not achieved or resistance is developed to first-line treatment in 20% to 30% of patients,[12] the availability of multiple products in the class is clinically important.

Data and Methods

Study Sample

We assembled a data set of all pharmacy and medical claims from 1997 to 2009 for 45 large, geographically diverse US employers. These data, obtained from a benefits consulting firm, have been used previously to explore the association of pharmacy benefit design with medication use by the chronically ill.[13,14] Each employer offered 1 or more health plans to its active or retired employees and their dependents. Each pharmacy claim included the medication name, dosage, days supplied, date and place of purchase (retail or mail order), patient out-of-pocket (OOP) expense, and health plan payment. Medical claims included information on the service type (eg, inpatient or emergency department [ED]) and date, billed charges, patient OOP expense, health plan payments, and associated diagnosis codes. Demographic variables included age, gender, the first 3 digits of the individual's zip code of residence, relationship to the primary beneficiary, and employment status of the primary beneficiary.

The study sample included a cohort of adult patients (aged ≥18 years) with an initial diagnosis of CML during 1997 to 2009. We identified individuals with CML based on the presence of 2 or more *International Classification of Diseases, Ninth Edition, Clinical Modification* (*ICD-9-CM*) diagnosis codes (primary, secondary, or tertiary) of 205.1x in the medical claims, or 1 *ICD-9-CM* code and use of TKI therapy after diagnosis. The requirement for a second CML diagnosis or the use of a TKI serves to filter out patients with "rule-out" diagnoses. We excluded patients with less than 1 year of follow-up data and with just 1 *ICD-9-CM* diagnosis for CML, as well as those with no claims for TKI therapy over their entire claims history. Because firms entered and exited the database over time, we did not have a complete panel on all individuals. The majority of members were observed for 2 to 4 years, with fewer than 10% of the sample followed for 7 years.

We defined 2 distinct study samples: 1) those newly diagnosed with CML, and 2) CML patients in whom use of a TKI was initiated. Patients were considered newly diagnosed if they had at least 1 year of data prior to the index date (date of their first *ICD-9-CM* code) without a claim for the condition; for example, individuals with 2 *ICD-9-CM* codes for CML in 2004 would be considered newly diagnosed if they had no other *ICD-9-CM* codes for the condition in prior years (eg, 1997-2003) if continuously enrolled. Similarly, we defined the TKI-initiation sample based on the absence of any TKI use in prior years. We focused on newly diagnosed patients because we had full information on the history of their condition and the treatments they had received for it.

Use of and Adherence to TKI Therapies

The aims of the study were to examine the ways in which TKIs are covered in private health plans, how demand responds to cost-sharing, and whether use of TKIs affects the use of other healthcare services. We measured adherence to TKI treatment as the proportion of days in which therapy was supplied; for example, if a patient filled 9 TKI prescriptions, each providing a 30-day supply, utilization was determined to be 74% (270/365). Not all CML patients who began a TKI regimen remained on therapy; nearly 3% of TKI users stopped therapy in the first year of treatment and more than 5% stopped at some point during the study period. For these patients utilization was measured from the date of initiation to their last day of supply. This approach yields a higher estimate of adherence but minimizes measurement error due to discontinuation of therapy.

Patient Characteristics

Because the data were derived from health claims and enrollment data, they contained a limited set of demographic covariates, including age, gender, marital status, and sponsorship status (employee or dependent type). Measures of health status were derived from the claims directly as a sequence of binary indicators for whether the patient had 2 or more claims for a specific condition during the year; 2 or more claims were required to avoid rule-out diagnoses. One virtue of such large data sets is that many comorbid conditions can be entered simultaneously as control variables. We included the following 30 comorbid conditions in the analyses: essential hypertension, congestive heart failure, diabetes, asthma, hypercholesterolemia, ulcer, depression, chronic obstructive pulmonary disease, allergic rhinitis, migraine, arthritis, chronic sinusitis, anxiety disorder, cardiac disease, vascular disease, epilepsy, gastric acid disorder, glaucoma, gout, hyperlipidemia, irritable bowel syndrome, malignancies other than CME, psychotic illness, thyroid disorder, rheumatoid arthritis, tuberculosis, angina, human immunodeficiency virus, anemia, and stroke.

Plan-Level Index of Generosity

Estimating the impact of patient cost-sharing requires measurement of benefit generosity at the plan level. Based on prior work[13] we characterized the OOP cost of TKI therapy by computing the mean OOP cost within a plan for the weighted basket of TKI medications available in that year, where the weights reflect the market share of TKIs across all plans in the sample year. This allowed for a direct comparison of the OOP costs associated with purchase of these medications across plans. We excluded plans with small numbers of TKI users and adjusted prices to constant dollars using the medical services consumer price index.

Empirical Approach: Estimating the Demand for TKI Therapy

We estimated the price sensitivity of TKI therapy using multivariate regression to correlate the utilization of therapy to the price of drug therapy in the plan. Specifically, we used the following linear probability model for individual j and year t:

$$Y_{jt} = \alpha + \delta_t + \beta_1 price_{jt} + \Gamma X_{jt} + \varepsilon_{jt}$$

In the above equation,

- Y_{jt} is the number of days' supply of TKIs by patient j in year t
- α is a constant parameter
- δ_t is a year fixed-effect
- β_1 is the price sensitivity parameter
- $price_{jt}$ is the average price per-claim for TKI therapies, which is calculated as the average OOP amount per claim among all persons using a TKI in individual j's plan in year t
- Γ is a vector of sensitivity parameters to individual characteristics
- X_{jt} is a vector of individual characteristics (including age, comorbidities, etc)
- ε_{jt} is the error term, which we cluster at the employer level, since the variation in price is at the plan level and plans are nested within employers.

We first estimated the probability of a patient initiating TKI therapy as a function of plan generosity, as well as adherence to TKI therapy, conditional on use. We measured adherence as the number of days supplied (or proportion of days covered, or cumulative medication gap in a time frame), conditional on initiating therapy. This structure imposed the restriction that the price sensitivity of TKI therapy is similar across the different medications. This seemed reasonable given that all 3 TKIs currently on the market are used to treat advanced forms of CML, and imatinib was the sole TKI until 2006. Moreover, pooling the data across TKIs allowed us to obtain more precise estimates than if we had focused on each medication alone—an important consideration given that some of the medications in our sample were used by only a small number of patients. We also estimated the impact of TKI therapy on medical spending and use. Estimates from the multivariate models were used to predict medical and prescription spending for TKI users and TKI non-users, controlling for individual and plan heterogeneity. More specifically, estimates from the models were used to predict annual spending by type of service for each person in the study sample. The models included controls for patient demographics (age, gender, marital status, employment status), comorbid conditions, time since diagnosis, geographic and socioeconomic measures (census region or state, urban residence, median household income in the zip code), and annual time dummies. In all models we adjusted our variance estimates to allow for correlation (or "clustering") of individuals within plans.

Sensitivity Analysis

To provide some context for our results, we looked at the impact of cost-sharing on the use of another oral cancer agent. Erlotinib is a kinase inhibitor used to treat non-small-cell lung cancer (NSCLC) and is also used as part of a combination regimen for pancreatic cancer. Erlotinib is widely

Table 1. Characteristics of Patients With Chronic Myeloid Leukemia

	Full Sample	TKI Users	TKI Non-Users
N/Person-years	995/3,765	415/1,689	580/2,076
Demographics			
Mean age (years)	61.9	62.2	61.8
Standard deviation	(14.0)	(13.2)	(14.7)
Male (%)	53.6	54.6	52.8
Standard deviation	(49.9)	(49.8)	(50.0)
Currently working (%)	32.2	29.0	34.7
Standard deviation	(46.7)	(45.4)	(47.7)
Years since CML diagnosis	2.4	2.4	2.4
Standard deviation	(2.5)	(2.4)	(2.5)
Number of comorbid conditions	3.4	3.3	3.4
Standard deviation	(2.5)	(2.4)	(2.5)
Utilization (annual)			
Percent hospitalized	33.2	30.6	35.3
Standard deviation	(47.1)	(46.1)	(47.8)
Outpatient visits	26.0	25.7	26.2
Standard deviation	(21.9)	(19.6)	(23.6)
Emergency department visits	0.69	0.65	0.72
Standard deviation	(1.8)	(1.5)	(1.9)
Medical expenditures ($)	34,240	26,565	40,492
Standard deviation	(84,957)	(57,703)	(101,472)
Prescription expenditures ($)	23,173	36,414	12,386
Standard deviation	(28,758)	(23,415)	(28,190)
Plan characteristics			
Average coinsurance rate, TKIs (%)	5.2	3.6	7.0
Standard deviation	(14.4)	(10.0)	(17.9)

CML indicates chronic myeloid leukemia; TKI, tyrosine kinase inhibitor. Sample means reflect averages across 3,765 person-years of data for the years 1997 to 2009. The average coinsurance rate for the plan is defined as the average ratio of patient out-of-pocket cost to total paid cost for TKIs.

used in the United States and costs $30,000 to $40,000 for a year of treatment. We looked at the impact of copayments on utilization of erlotinib to provide a point of comparison.

Finally, we examined the sensitivity of our results against more stringent definitions of CML by excluding individuals with CML diagnosis codes who were not taking any medications for CML.

Results

Our sample included 995 patients newly diagnosed with CML (Table 1). Since data were available for these individuals for multiple years after diagnosis, the number of person-years (number of individuals multiplied by number of years in the data post-diagnosis) is considerably larger (N = 3,765). More than 80% (812) of patients in the study sample were diagnosed with CML after the introduction of imatinib in 2001, with 42% (415) having filled at least 1 prescription for a TKI over the study period. The majority of patients were observed for 3 or more years. The demographic characteristics of CML patients who initiated use of a TKI were similar to those of non-users, although non-users were more likely to be working than were users (34.7% vs 29.0%). This suggests that differences in health outcomes between the 2 groups are more likely to result from TKI use than from preexisting demographic differences. Both groups frequently utilized healthcare services, with the average CML patient making 26 outpatient visits per year and accruing total annual expenditures in excess of $50,000. Even so, the distribution of spending varied substantially. TKI users incurred higher total healthcare costs than non-users; specifically, these patients spent considerably more on pharmaceuticals and less on medical services

Table 2. Coverage and Adherence to TKI Therapies

	Mean	Median	75th Percentile	90th Percentile
Payments (per script)				
Patient out-of-pocket ($)	56	25	63	122
Total ($)	3,842	3,747	4,647	5,426
Adherence				
Medication possession ratio (MPR)[a]	85.7	94.8	100.0	100.0

TKI indicates tyrosine kinase inhibitor.
[a]Measurement of MPR can vary depending on how the end date is defined. In this case, we measure MPR from the date of first TKI use through the last recorded fill date of any TKI therapy. This approach excludes nonadherence due to cessation of therapy. A total of 2.5% of TKI users stopped therapy in the first year of treatment, whereas 5.3% of TKI users stopped therapy at some point in the study period.

than non-users. Non-users were enrolled in health plans with less generous coverage of TKIs but, overall, average coinsurance rates were low.

Although TKI therapies are expensive, they were generously covered in most of the employer-sponsored plans in our sample (Table 2). A 30-day supply of a TKI costs $4,000 to $8,000, yet the median copayment in our sample was just $25. The least generous plans, with copayments of $100 or more per 30-day supply, had an average coinsurance rate of less than 5%. However, even generous cost-sharing at the plan level can translate into significant OOP expenses for CML patients, given the cost of these treatments. For example, mean annual OOP costs in the sample were $2,779, with $785 attributable to medications. Further, 1 in 4 CML patients had total OOP costs in excess of $7,000.

Given the efficacy of these therapies and the low level of patient cost-sharing, it is not surprising that adherence was high. The average medication possession ratio for TKIs was 85.7%, which suggests that CML patients had the TKI on hand roughly 7 out of 8 days. More importantly, we found no statistically significant relationship between generosity of coverage and use of TKI therapies, measured either as initiation of TKI therapy or adherence conditional on use. CML patients with less generous coverage were more likely to stop therapy. This effect was statistically significant, although quite modest in size. It is notable here that no plans charged copayments in excess of $200, and only a small number charged copays higher than $100. The lack of extreme cost-sharing is likely to mute the effect of cost-sharing on initiation of treatment.

Table 3 shows adjusted estimates of annual spending for TKI users and non-users based on multivariate models that control for individual and plan heterogeneity. Pharmaceutical spending was considerably higher among TKI users. CML patients using TKIs spent $26,452 more on medications than similar patients who did not begin treatment with a TKI (in 2009 dollars). However, average annual medical expenditures were $11,788 lower, offsetting nearly 45% of the incremental costs in medication spending. In sum, the use of TKIs increased total expenditures at a relatively modest cost per life-year and shifted the distribution of healthcare spending. Specifically, as discussed in the second article in this supplement by Yin et al,[15] the introduction of TKIs led to a 10-year gain in median survival, from 7.5 years to 17.5 years. The incremental annual cost of TKI use is just under $15,000. Over a 17.5-year horizon, with a 3% real rate of discount, an annual flow of $15,000 in net costs has a net present value of $206,000. Thus, this rough "back-of-the-envelope" calculation suggests that the incremental cost-effectiveness ratio is less than $20,600 per life-year gained, which would be considered cost-effective by conventional standards.

Sensitivity Analyses

Given the generosity of coverage for TKIs and the lack of variation across plans, we looked at the coverage of other oral cancer agents to assess the impact of high patient cost-sharing on use. As previously noted, the kinase inhibitor erlotinib is used for the treatment of NSCLC and as part of a combination regimen for the treatment of pancreatic cancer and costs $30,000 to $40,000 for a year of treatment. The mean copayment in our sample was $124, with the least generous plans (top decile) charging members $224 or more for a 30-day supply. Table 4 shows the adjusted impact of copayments on the annual days of supply for erlotinib. For lung cancer patients using erlotinib, annual days supplied was 15% lower for those paying $200 or more, relative to similar patients with copayments less than $100 per 30-day prescription.

Some individuals in our sample were classified as having CML based on 2 or more *ICD-9-CM* diagnosis codes, but were not taking TKIs or other medication for the condition. We re-estimated the models excluding these patients to

Table 3. Predicted Annual Medical and Prescription Spending by TKI Use

Annual Spending	TKI User (A)	TKI Non-User (B)	Difference (A-B)
Medical ($)	26,406	38,194	–11,788
Prescriptions ($)	39,126	12,674	+$26,452
Total ($)	65,532	50,868	+14,664

TKI indicates tyrosine kinase inhibitor.

assess the extent of this misclassification bias. Although the overall results were substantively unchanged, the magnitude of effect increased in some specifications. For example, 58% of CML patients were taking a TKI, which was more in line with current levels of treatment. In addition, TKI use was associated with even larger reductions in medical spending (38%) when potentially misclassified CML patients were excluded.

Discussion

Cost-sharing has been viewed as a way to protect against moral hazard and discourage overconsumption of services with little social value. One difficulty, of course, is identifying the services that are cost-saving or cost-effective and then ensuring that cost-sharing policies are sufficiently generous to encourage their use.

We found that use of TKIs was associated with lower spending on other types of healthcare services. CML patients on TKI therapy had roughly $12,000 less in non-pharmaceutical medical costs than did patients on alternative forms of therapy. This translated into a decline of more than 30% in medical spending and offset roughly 40% of the cost of TKIs. This result is consistent with prior work that suggested changing generosity for one healthcare service has both short- and long-term implications for spending in other areas. Chandra et al[16] found substantial off-setting increases in hospitalizations when copayments for outpatient and pharmaceutical use were increased. In this case, the cost of hospitalizations was borne by Medicare while the benefits of the reduction in prescription use accrued to the state's supplemental retiree plan. Similarly, Gaynor et al[17] found that while increased copayments for prescription medications reduced prescription utilization and spending, consumers spent more on other outpatient care.

Table 4. Predicted Use of Erlotinib at Different Copayment Levels

Copayment (for a 30-Day Supply)	Annual Use (Average Days Supplied)
Less than $100	202
$100 or more	184
$200 or more	171

Current TKI coverage policies appear to support the continued diffusion and use of these products. While the medications cost approximately $4,000 per month, the median copayment for a 30-day supply of TKIs was $25, and only a few plans charged members more than $100 per prescription. Further, neither initiation nor use of TKIs was related to cost-sharing. Patient adherence to prescribed medication regimens was high, perhaps reflecting the generosity of insurance coverage and the efficacy of these agents. By contrast, other oral cancer agents are not covered as generously and can serve as cautionary examples of the demand response if cost-sharing increases beyond certain thresholds. Copayments of $200 or more per month for erlotinib, an analogous oral agent used to treat lung cancer, were associated with a 15% reduction in use relative to those with copayments less than $100. Thus far, copay burdens of this magnitude are absent for TKIs. If they were to appear and exert downward pressure on adherence of the sort observed in the case of erlotinib, the evidence suggests that adverse health outcomes would result.[18]

A key challenge in this type of analysis is that disease severity cannot be measured directly, and patients who are more severely ill may use different types of therapies. Ideally, we would want to instrument for TKI use with the generosity of plan coverage, but, as noted earlier, there was limited variation in cost-sharing across plans in our sample. We attempted to minimize bias by selecting a more homogenous cohort of patients newly diagnosed with CML. Although this reduced our sample size by nearly 40%, we had full information on the history of the condition and the treatments received by these patients. Further, we found no significant differences between TKI users and non-users with regard to number of comorbid conditions or the probability of being hospitalized or admitted to the ED during their first year in the database. An additional limitation of our study was that the sample of CML patients, although large for this condition, was not representative of all privately insured patients or CML patients nationally. Lastly, our measure of medication utilization, days supplied, may have overstated actual adherence to TKI therapies, although this measurement error should not vary systematically across health plans.

Conclusions

The continued introduction of effective, high-cost, novel cancer therapeutics and diagnostics is likely to exert

increasing financial pressure on patients, oncologists, payers, businesses, and society, while simultaneously improving outcomes and expanding treatment options. Payers will have more latitude with which to vary the benefit designs offered to patients with cancer, and these decisions are likely to have significant health consequences. The solution is a more evidence-based approach to the design of insurance benefits. It will become critical to identify the value to patients of new therapies themselves, and of generous coverage for these therapies. Greater importance will thus be placed on evidence of value, and pressure will grow for payers to connect reimbursement and cost-sharing more directly to this evidence.

TKIs in particular have generated substantial health improvements for patients with CML; for instance, the evidence presented in this study suggests that their use has decreased medical care utilization by more than 30%. Payers appear to have recognized this value insofar as they have insulated TKIs from the more extreme cost-sharing requirements that have been placed on other oncology agents. This decision likely explains why adherence to TKIs is relatively high compared with other oncology agents. Taken together, these facts suggest that TKI coverage represents an important and instructive success story, in which benefit design is connected to value.

Author affiliations: Bristol-Myers Squibb, Plainsboro, NJ (TD, JRM); Leonard D. Schaeffer Center for Health Policy and Economics, and School of Pharmacy, University of Southern California, Los Angeles, CA (GFJ); Leonard D. Schaeffer Center for Health Policy and Economics, Sol Price School of Public Policy, and School of Pharmacy, University of Southern California, Los Angeles, CA (DG); Leonard D. Schaeffer Center for Health Policy and Economics, University of Southern California, Los Angeles, CA (DNL).

Funding source: This supplement was supported by Bristol-Myers Squibb.

Author disclosures: Dr Darkow and Dr Maclean report employment with and stock ownership in Bristol-Myers Squibb. Dr Goldman and Dr Lakdawalla report consultancy with Bristol-Myers Squibb and partnership in Precision Health Economics. Dr Joyce reports consultancy with Precision Health Economics.

Authorship information: Concept and design (TD, DG, GFJ, DNL, JRM); acquisition of data (DG, GFJ, DNL); analysis and interpretation of data (TD, DG, GFJ, DNL, JRM); drafting of the manuscript (TD, DG, GFJ, DNL, JRM); critical revision of the manuscript for important intellectual content (TD, DG, GFJ, DNL, JRM); statistical analysis (GFJ); obtaining funding (TD, GFJ, JRM); and supervision (JRM).

Address correspondence to: Dana Goldman, PhD, Leonard D. Schaeffer Center for Health Policy and Economics, University of Southern California, 3335 S Figueroa St, Unit A, Los Angeles, CA 90089-7273. E-mail: dpgoldma@healthpolicy.usc.edu.

REFERENCES

1. Schickedanz A. Of value: a discussion of cost, communication, and evidence to improve cancer care. *Oncologist*. 2010;15(suppl 1):73-79.

2. Aitken M, Berndt ER, Cutler DM. Prescription drug spending trends in the United States: looking beyond the turning point. *Health Aff (Millwood)*. 2009;28(1):w151-w160.

3. Hargrave E, Hoadley J, Merrell K. Drugs on specialty tiers in part D. 2009; No. 09-1. http://www.medpac.gov/documents/feb09_drugsonspecialtytiers_contractor_rs.pdf. Accessed October 13, 2012.

4. Kaiser Family Foundation. Medicare part D 2010 data spotlight: coverage of top brand-name and specialty drugs. http://www.kff.org/medicare/upload/8095.pdf. Published 2010.

5. Kocs D, Fendrick AM. Effect of off-label use of oncology drugs on pharmaceutical costs: the rituximab experience. *Am J Manag Care*. 2003;9(5):393-400.

6. Erba HP, Pham DC, Zaiden R, Vu H, Tai S. Improving frontline treatment for chronic myeloid leukemia: emerging evidence for use of nilotinib and dasatinib. *Clin Adv Hematol Oncol*. 2011; 9(10):734-745.

7. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2010;362(24):2260-2270.

8. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010;362(24):2251-2259.

9. Lee J. Research and development related to dasatinib (Sprycel). KEI Research Note 2008:3. http://www.keionline.org/misc-docs/research_notes/kei_rn_2008_3.pdf. Published July 7, 2008. Accessed October 22, 2012.

10. Arora A, Scholar EM. Role of tyrosine kinase inhibitors in cancer therapy. *J Pharmacol Exp Ther*. 2005;315(3):971-979.

11. Westin JR, Kantarjian H, Kurzrock R. Treatment of chronic myelogenous leukemia as a paradigm for solid tumors: how targeted agents in newly diagnosed disease transformed outcomes. In: *2012 ASCO Annual Meeting Educational Book*. American Society of Clinical Oncology: 2012; Alexandria, VA.

12. Quintas-Cardama A, Kantarjian HM, Cortes JE. Mechanisms of primary and secondary resistance to imatinib in chronic myeloid leukemia. *Cancer Control*. 2009;16(2):122-131.

13. Karaca-Mandic P, Jena AG, Joyce GF, Goldman DP. Out-of-pocket medication costs and use of medications and health care services among children with asthma. *JAMA*. 2012;307(12):1284-1291.

14. Goldman DP, Joyce GF, Escarce JJ, et al. Pharmacy benefits and the use of drugs by the chronically ill. *JAMA*. 2004;291(19): 2344-2350.

15. Yin W, Penrod JR, Maclean JR, et al. Value of survival gains in chronic myeloid leukemia. *Am J Manag Care*. 2012;18:S257-S263.

16. Chandra A, Gruber J, McKnight R. Patient cost-sharing and hospitalization offsets in the elderly. *Am Econ Rev*. 2010;100(1): 193-213.

17. Gaynor M, Li J, Vogt W. Substitution, spending offsets, and prescription drug benefit design. *Forum Health Econ Pol*. 2007; 10(2):1-31.

18. Darkow T, Henk HJ, Thomas SK, et al. Treatment interruptions and non-adherence with imatinib and associated healthcare costs: a retrospective analysis among managed care patients with chronic myelogenous leukaemia. *Pharmacoeconomics*. 2007;25(6):481-496.