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What Happens When Imatinib Goes Generic?

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Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of chronic myelogenous leukemia (CML). Current guidelines do not specify which of the 3 TKIs approved for the first-line treatment of chronic phase CML are preferred, and no evidence from clinical trials is available to support the superiority of second-generation TKIs dasatinib or nilotinib over imatinib with respect to survival outcomes. With current prices of TKIs around \$100,000 for a 1-year supply,¹ the out-of-pocket cost for these drugs is substantial and the long-term use of these medications may pose a financial burden for cancer survivors. Generic imatinib, expected to become available in 2016, will offer a lower-cost option for the treatment of CML, and thus the possibility to increase adherence and reduce patient financial burden. The TKI imatinib forever changed the treatment of CML. Before the approval of imatinib in 2001, allogeneic transplantation offered the only “curative” therapeutic approach, and 5-year survival in the pre-TKI era was less than 50%.² The introduction of imatinib, followed by the approval of the “second-generation” TKIs nilotinib and dasatinib in 2010, also for first-line therapy, and the recent addition of 2 second-line TKIs, bosutinib and ponatinib, for cases intolerant or resistant to first-line agents, have drastically improved the prognosis for patients with CML. Today patients with CML may expect to live close to normal lifespans,³ with an annual all-cause mortality of only 2%.⁴

The impressive survival gains observed over the past 15 years in CML have come with substantial cost, however. Patients with CML and their families often suffer from “financial toxicity.”⁵ The financial burden and distress associated with TKI therapy for the treatment of CML has become so severe that numerous doctors have raised objections to the soaring prices of imatinib and its second-generation alternatives.⁶

Lower-cost TKI therapy may soon be available, as the patent for imatinib is due to expire in early 2016, and generic imatinib is expected to enter the marketplace soon after. With the arrival of a generic TKI, clinicians—and presumably guideline-making bodies—will need to embrace the economics of CML treatment as a very real issue that needs to be included in treatment decisions.

NCCN and the LeukemiaNet (ELN) guidelines for treating CML do not specify which of the approved first-line TKIs—imatinib, nilotinib, or dasatinib—are preferred for patients with newly diagnosed chronic phase CML.^{7,8} There is some logic behind this agnostic stance:

- **All TKIs work well in chronic phase.** The complete cytogenetic response (CCyR) rates among patients treated with imatinib are approximately 70% and 90% at 1 year and 5 years, respectively.⁹ After 8 years of follow-up, approximately 90% of patients treated with imatinib on the IRIS (International Randomized Study of Interferon and STI571) trial were still alive.¹⁰ However, results from 3 randomized trials (2 pharmaceutical and 1 US Intergroup) have consistently shown that rates of CCyR are even higher (roughly 10 percentage points) with the second-generation TKIs nilotinib and dasatinib.^{11–13} Other relevant measures of response are also better with second-generation TKIs, such as reaching a major molecular response (MMR), complete molecular response (CMR), and progression to advanced phase disease. However (and surprisingly), these superior responses have not translated into overall survival differences. Even with more than 5 years of follow-up, the survival rates between the imatinib and dasatinib/nilotinib arms are statistically similar in all studies.

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- **TKI failures are not unusual.** Only 60% of patients treated with imatinib on the IRIS trial remained on drug and in CCyR,¹⁴ with failures near equally divided into tertiles of primary resistance, toxicity, and resistance/progression. In patients for whom front-line imatinib fails, salvage therapy with the second-generation TKIs (dasatinib, nilotinib) can yield a CCyR in 40% to 50% of cases.^{15,16} For patients in whom initial therapy with a second-generation agent fails, salvage with another second-generation TKI or a “third-generation” agent (bosutinib or ponatinib), can yield major and complete cytogenetic remission, but generally at a lower frequency.^{17–19} However, patients with initial response to second-line therapy often experience relapse, sometimes with a new mutation. Patients in this category can be treated with other TKIs (bosutinib, ponatinib), but if one is looking for cure, allogeneic transplantation remains the best bet for highly resistant disease.^{20,21}
- **The stronger potency of second-generation agents comes with new toxicities.** It appears that the more potent second-generation TKIs have unique adverse events, including vascular occlusion events (ponatinib, nilotinib), pulmonary artery hypertension and pleural effusions (dasatinib), pancreatitis (ponatinib), hypertension (ponatinib), hyperglycemia (nilotinib), and diarrhea (bosutinib). In contrast, the long-term follow-up of patients treated with imatinib has not revealed any new late adverse effects. In the NCCN and ELN guidelines, consideration is given to potential toxicity given a patient’s particular comorbidities, as well as clinical score (Sokal or Hasford), with some concern for using more potent agents in patients with higher scores, assuming these patients have more disease and may be closer to disease progression. Another consideration is the ability to reach a deep or complete molecular remission, because a subset of patients who experience this remission can discontinue therapy. This might be especially important in younger patients, who may wish to have children.

Currently, NCCN and ELN guidelines make no mention of the cost of these TKIs, although numerous initiatives are underway to include discussions of value in clinical guidelines.^{22,23} Health care reform, including the passage of the Affordable Care Act, value-based payment programs, clinical pathways, and increased public and political awareness of financial toxicity, demonstrate that the future of health care in the United States is one in which a patient’s financial situation should be considered when making decisions about therapy selection.

Reducing patient financial burden through the use of generic imatinib may improve outcomes for patients with CML. The mean per patient out-of-pocket costs for a 30-day supply of imatinib, nilotinib, and dasatinib in 2013 was \$78 (range, \$0–\$7,297), \$98 (range, \$0–\$9,328), and \$79 (range, \$0–\$9,663) respectively (data from Truven Health Analytics; <http://truvenhealth.com>). A recent study by Dusetzina et al²⁴ found that patients with CML with out-of-pocket costs in the 75th percentile (mean of \$53) were 70% more likely to discontinue therapy and were 42% more likely to be nonadherent. Nonadherence and discontinuation are directly associated with poorer outcomes. In studies of long-term imatinib users, poor adherence has been associated with a significantly reduced probability of achieving an MMR or a CCyR and a higher probability of losing a CCyR.^{25,26} In patients who had a treatment interruption longer than 1 week, Ganesan et al²⁷ estimated a 5-year event-free survival of 59.8% compared with 76.7% among patients without that interruption, showing that poor adherence is associated with worse survival.

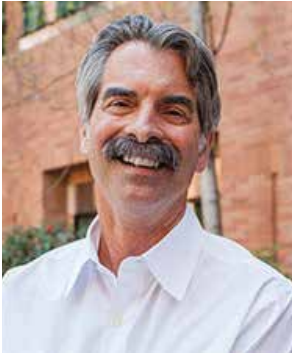
High out-of-pocket costs for TKIs are a function of both the high cost of the drugs themselves and the response by public and private insurers of placing TKIs on specialty



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tiers that require higher copays and coinsurance than lower-cost pharmaceuticals. When imatinib goes generic, the cost should drop substantially and insurers may cover the generic version more favorably. Litigation between Novartis and a subsidiary of Sun Pharmaceutical Industries Ltd. settled in 2014, permits Sun Pharma's subsidiary to market generic imatinib in the United States beginning in February 2016. The FDA has awarded Sun Pharma tentative approval and 6 months' market exclusivity after patent expiration. Typically, during the exclusivity period, generic drugs are priced at 70% to 90% of branded prices.²⁸ The magnitude of the price reduction after the exclusivity period depends on the number of generic competitors entering the market, with generic drug prices on average 43% lower than branded drug prices, but up to 85% lower than branded drugs when 3 or more competitors are on the market. In Canada, where 2 generic versions of imatinib have been available for several years, the price for generic imatinib is between 18% and 26% of the branded price.²⁹ Given Novartis' secondary patents, including those for pediatric formulations of imatinib, it is possible that competition will be limited until all patents expire in 2019.³⁰ However, even a reduction in price of 10% would equate to nearly \$1,000 off the wholesale price per 30-day supply. This would make generic imatinib substantially less costly than other TKIs for CML.

Widespread adoption of generic imatinib will depend on patient preference, health system incentives, and physician willingness to prescribe the generic version.³¹ In our view, the advent of generic imatinib provides the opportunity to reduce the financial burden to patients of treating CML. In reducing the financial burden, generic imatinib may improve clinical outcomes as more patients are able to access and adhere to the medication. If the reduction in out-of-pocket costs is substantial enough to move average adherence above 90%, the risk of loss of cytogenetic response will likely decrease and time to progression will likely increase. Moreover, the clinical and economic costs related to treating relapses in patients with poor adherence may be avoided.

Given the current state of clinical evidence and the demonstrated role that financial toxicity plays in long-term adherence, we believe that the benefits of using generic imatinib warrants its selection over branded TKIs for initial treatment in the majority of patients with CML.

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