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

Experts in Chronic Myeloid Leukemia

As a group of more than 100 experts in chronic myeloid leukemia (CML), we draw attention to the high prices of cancer drugs, with the particular focus on the prices of approved tyrosine kinase inhibitors for the treatment of CML. This editorial addresses the multiple factors involved in cancer drug pricing and their impact on individual patients and health care policies, and argues for the need to (1) lower the prices of cancer drugs to allow more patients to afford them and (2) maintain sound long-term health care policies. (*Blood*. 2013;121(22):4439-4442)

The doctrine of *justum pretium*, or just price, refers to the "fair value" of commodities. In deciding the relationship between price and worth (or value), it advocates that, by moral necessity, price must reflect worth. This doctrine may be different from the doctrine of free market economies where prices reflect "what the market bears," or what one is willing to pay for a product. Which doctrine is better? One could argue that when a commodity affects the lives or health of individuals, just price should prevail because of the moral implications. Examples include the price of bread during famines, polio vaccine, ivermectin for river blindness (provided for free by Merck and estimated to have saved the vision of 30 million individuals), and treatments of chronic medical conditions (cardiovascular, hypertension, diabetes, tuberculosis, multiple sclerosis, etc). When commodities are not essential to life or suffering, what the market will bear is appropriate (competition will take care of price) because it is not restrained by ethical considerations. Examples include the price of a Picasso painting, a luxury cruise, a 2-week vacation in New York (or 4 weeks in Houston), a Bentley car, a Brioni suit, etc.

Through positive collaborations with Pharma, experts in chronic myelogenous leukemia (CML) have been fortunate to have 3 drugs approved by the US Food and Drug Administration (FDA) in 2012 for the treatment of CML: bosutinib, ponatinib, and omacetaxine. This is in addition to 3 others approved in the last decade: imatinib, dasatinib, and nilotinib. The 3 new drugs, however, have been priced at astronomical levels: ponatinib at $138 000 per year, omacetaxine at $28 000 for induction and $14 000 per maintenance course, and bosutinib at ~$118 000 per year.[1]

Cancer drug prices have been discussed recently by some financial analysts and tend to be discussed whenever new cancer drugs are approved. This Forum reflects the views of a large group of CML experts who believe that the current prices of CML drugs (1) are too high, (2) are unsustainable, (3) may compromise access of needy patients to highly effective therapy, and (4) are harmful to the sustainability of our national health care systems. These concerns reflect the spiraling prices of cancer drugs in general. Of the 12 drugs approved by the FDA for various cancer indications in 2012, 11 were priced above $100 000 per year. Cancer drug prices have almost doubled from a decade ago, from an average of $5000 per month to >$10 000 per month.[2]

Innovation and discoveries must be rewarded. Pharmaceutical companies that invest in research and development and discover new lifesaving drugs should benefit from healthy revenues. The cost for bringing a new cancer drug to market is reported to be ~$1 billion.[3] This much-argued-about figure, which some independent experts put as low as $60 to 90 million,[4] includes the cost of development of the new (successful) drug and all other drugs that failed during development, and ancillary expenses including the cost of conducting the clinical trials required for approval, bonuses, salaries, infrastructures, and advertising among others. In other words, once a company sells about a billion dollars of a drug, most of the rest is profit.

How are the prices of cancer drugs decided? Of the many complex factors involved, price often seems to follow a simple formula: start with the price for the most recent similar drug on the market and price the new one within 10% to 20% of that price (usually higher). This is what happened with imatinib, priced in 2001 at $2200 per month, based on the price of interferon, which was then the standard treatment.[5]

If drug price reflects value, then it should be proportional to the benefit to patients in objective measures, such as survival prolongation, degree of tumor shrinkage, or improved quality of life. For many tumors, drug prices do not reflect these end points because most anticancer drugs provide minor survival benefits, if at all. For example, in pancreatic cancer, where the median survival is 6 months, a new drug that may prolong survival by 2 months and is priced at $100 000 per year will cost $67 000 over 8 months survived, or $33 500 per additional month lived, equivalent to $400 000 per additional year lived. Similar calculations can be made for other cancers depending on the expected median survival, additional time lived, and therefore the price of an additional year lived. By these measures, the price of cetuximab was valued at ~$800 000 per

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Experts in Chronic Myeloid Leukemia contributed equally to this study and are cited in "Appendix."

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year of increased survival.[2] In many countries, an additional year lived is judged to be "worth" ~$50 000 to $100 000.[6,7] In England, the National Institute for Health and Clinical Excellence values a year lived at about 30 000 British pounds, or ~$50 000.

The situation in CML is different. When imatinib was approved in 2001, its potential benefit in prolonging life was unknown. Considering a median survival of ~5 to 6 years in the pre-imatinib era, a 50% improvement in survival would have extended life by 3 years, which was then a very optimistic outlook. Therefore, the original imatinib price of $30 000 in 2001 may have reflected the cost of development and a projection of anticipated survival, using the price of interferon, the approved commercial drug for CML, as a starting point. In his book, Daniel Vasella, then Chairman and Chief Executive Officer of Novartis, discussed the development of imatinib, the moral imperatives and pressures exerted by oncologists and patients, the need for healthy profit margins, and the decision to price imatinib at a world average of $2200 per month, or $26 000 per year ($30 000 per year in the United States).[5] This, he explained, was considered at the time a high but worthwhile and profitable price. With a prevalence of 30 000 patients in the United States (the effect of imatinib on the prevalence of CML was then difficult to estimate) and full market penetration (ie, most patients with CML receiving imatinib), the annual revenue from imatinib sales in the United States would be ~$900 million, which would have more than recouped the cost of development within 2 years. The revenues over the subsequent years of the patent would represent generous profits to the company.

Imatinib and the new Bcr-Abl tyrosine kinase inhibitors (TKIs) became the most successful class of targeted therapies ever developed in cancer, exceeding all projected survival expectations. With TKI therapy, the annual all-cause mortality in CML declined to 2%, vs a historical rate of 10% to 20%, and the estimated 10-year survival increased from <20% to >80%.[8] Patients with CML now live close to normal lifespans,[9] as long as they receive the appropriate TKIs and adhere to treatment. Their CML condition has become very different from solid cancers, and more similar to indolent disorders like diabetes, hypertension, and cardiovascular disorders, where daily therapy is required indefinitely to produce the anticipated benefit of long-term survival. Grateful patients may have become the "financial victims" of the treatment success, having to pay the high price annually to stay alive.

In Europe and many developed countries, universal health coverage shields patients from the direct economic anxieties of illness. Not so in the United States where 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), and where medical illnesses and drug prices are the single most frequent cause of personal bankruptcies.[10] High drug prices may be the single most common reason for poor compliance and drug discontinuation, and the reason behind different treatment recommendations in different countries.

Cancer drug prices vary widely in different geographic regions (Table 1[11,12]). This supports the notion that drug prices reflect geopolitical and socioeconomics dynamics unrelated to the cost of drug development. In the United States, prices represent the extreme end of high prices, a reflection of a "free market economy" and the notion that "one cannot put a price on a human life," as well as a failure of government and insurers to more actively negotiate pricing for anticancer and other pharmaceuticals, in contrast to practices in other parts of the world. This contributes to the very high cost of health care in the United States, estimated at $2.7 trillion in 2011, or 18% of the US gross domestic product, compared with 6% to 9% in Europe.[13] This increased expenditure does not add demonstrable benefit to US patients.[14] At the other extreme are more modest prices in the Middle East, Africa, Latin America, and other emerging nations, where only a minority of patients can afford, as individuals or through government subsidies, to access the CML drugs. In many emerging nations where governments cannot afford to budget for such drugs, CML experts are advocating frontline allogeneic stem cell transplantation because it costs an average of $30 000 to $80 000 as a one-time procedure.[15] This may harm patients because only a fraction may be eligible for transplantation (and may suffer from early mortality and lifelong complications); a smaller fraction are rich enough to pay individually for the price of the drugs, and most are treated intermittently or not at all. The effects of these financial pressures on the long-term survival of patients with CML in national follow-up studies are as yet unknown.

Table 1. Annual price estimates, by region, of drugs approved for the treatment of CML

Country	Price in thousands of US dollars (rounded to nearest $0.5 thousand)		
	Imatinib	Nilotinib	Dasatinib
United States	92	115.5	123.5
Germany*	54	60	90
United Kingdom	33.5	33.5	48.5
Canada	46.5	48	62.5
Norway	50.5	61	82.5
France	40	51.5	71
Italy	31	43	54
South Korea	28.5	26	22
Mexico	29	39	49.5
Argentina	52	73.5	80
Australia	46.5	53.5	60
Japan	43	55	72
China	46.5	75	61.5
Russia	24	48.5	56.5
South Africa	43	28	54.5

Prices in the United States from the Red Book online.[1] Other prices provided by CML experts from their countries.

*In Germany, a new rule, the "Pharmaceutical Market Restructuring Act" or AMNOG (arzneimittelneuordnungsgesetz), took effect in January 2011, by which the prices of new drugs are negotiated according to their benefit in comparison with other drugs on the market for the same indication. Similar rules or laws are also in effect in other European countries.[11] Prices of drugs in Germany may directly or indirectly influence drug prices in 31 countries.[12]

Imatinib was developed as a "goodwill gesture" by Novartis and became a blockbuster, with annual revenues of ~$4.7 billion in 2012. Being one of the most successful cancer targeted therapies, imatinib may have set the pace for the rising cost of cancer drugs. Initially priced at nearly $30 000 per year when it was released in 2001, its price has now increased to $92 000 in 2012,[1] despite the fact that (1) all research costs were accounted for in the original proposed price,[5] (2) new indications were developed and FDA approved, and (3) the prevalence of the CML population continuing to take imatinib was dramatically increasing.[16] This resulted in numerous appeals by patients and advocates to lower the price of imatinib, to no avail so far.[17,18]

What determines a morally justifiable "just price" for a cancer drug? A reasonable drug price should maintain healthy pharmaceutical company profits without being viewed as "profiteering" (making profit by unethical methods, like raising commodity prices after natural disasters). Hillner and Smith suggested this term may apply to the trend of high drug prices, where a life-threatening medical condition is the disaster.[19] Hopes that the fundamentals of a free market economy and market competition will settle cancer

drug prices at lower levels have not been fulfilled. All 5 TKIs approved for CML have annual price ranges of $92 000 to $138 000 in the United States, twice the prices in Europe where governments bargain for bulk prices (Table 1). A new branch of economics, called game theory, details how collusive behavior can tacitly maintain high prices over extended periods of time, despite competitive markets, thus representing a form of "collective monopoly."[20] Interestingly, in South Korea, where annual prices for TKIs range from $21 000 to $28 000, market competition may have worked well, perhaps because of the approval by the Korean health authorities of radotinib (annual prices $21 500), a locally discovered and developed TKI.

The patent expiration date of imatinib, originally set in the United States for May 28, 2013, was later extended by the US Patent Office to January 2015. Patent expiration dates may be different in different countries/regions. Two years is still a long time for patients with CML, the prevalence of which is estimated today worldwide at ~1.2 million to 1.5 million patients. Based on sales, it is estimated that about 235 000 to 250 000 patients (<20%-25%) are receiving imatinib. Support programs like the Glivec International Patient Assistance Program, a joint effort of Novartis and The Max Foundation, provide access to about 60 000 patients, perhaps ~30 000 to 40 000 of whom have CML (Glivec International Patient Assistance Program providing TKIs to 1%-3% of the world's CML population).[21] Thus, treatment penetration of TKIs in CML may be ~25% to 30% globally. When treatment penetration and compliance rates are high (such as in single institutional studies, in cooperative group trials, and in Sweden), the estimated 10-year survival rates are >80%.[8,9,22] When treatment penetration may be lower, outcome may be worse. In the United States, ~10% of patients fail to take prescribed drugs, largely because of cost.[23] Trends of CML survival in the United States show an improvement since 2001, but the estimated 5-year survival rate is still ~60%, suggesting lower treatment penetration rates in the United States compared with Sweden.[22,24] Unaffordable CML drug prices may be preventing many patients from accessing these lifesaving drugs. Lowering the prices of TKIs will improve treatment penetration, increase compliance and adherence to treatment, expand the population of patients with CML who live longer and continue on TKI therapy, and (paradoxically) increase revenues to pharmaceutical companies from sales of TKIs.

Early introduction of generics has been estimated to have saved the US health care budget about $1.1 trillion over 10 years.[25] In leveraging drug prices, companies may engage in "pay-for-delay" strategies that delay generic drugs from being available. Arrangements by pharmaceutical companies that pay generic companies to delay entering the market with a generic version profit both companies, but financially hurt the national health care system and patients. The Hatch-Waxman Act provides a 6-month market exclusivity for the first FDA-approved generic version of a branded drug. The intent of the act is to encourage the rapid launch of low-cost generics and reduce health care costs. Other generics can be marketed afterward. By launching their own generics (called "authorized generics") at low prices, branded drug companies have diminished generic company profits, resulting in delays of access of generics and reduced competition.[26] Delays of generic TKIs through "pay-for-delay" or "authorized generic" approaches may harm patients with CML and should be avoided at all cost.

As physicians, we follow the Hippocratic Oath of "*Primum non nocere*," first (or above all) do no harm. We believe the unsustainable drug prices in CML and cancer may be causing harm to patients. Advocating for lower drug prices is a necessity to save the lives of patients who cannot afford them. Pricing of cancer and other drugs involves complex societal and political issues which (1) demand immediate attention and (2) will need to consider many factors and involve many constituencies including FDA and governmental regulators; legislation changes; patent laws; multitudes of US and international regulatory agencies; offices of human research protection; impediments by lawyers and contract research organizations, which increase the cost of clinical research; patient advocacy groups; excessive regulation and bureaucracy; profits of physicians and hospitals/pharmacies; insurance companies; pharmaceutical companies; etc.

We propose to begin the dialogue by organizing regular meetings, involving all parties concerned, to address the reasons behind high cancer drug prices and offer solutions to reduce them. For CML, and for other cancers, we believe drug prices should reflect objective measures of benefit, but also should not exceed values that harm our patients and societies.

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Authorship

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A complete list of the Experts in Chronic Myeloid Leukemia appears in "Appendix."

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Appendix

The Experts in Chronic Myeloid Leukemia are listed by region below.

North America

Camille Abboud; Ellin Berman; Adam Cohen; Jorge Cortes; Daniel DeAngelo; Michael Deininger; Steven Devine; Brian Druker; Amir Fathi; Elias Jabbour; Madan Jagasia; Hagop Kantarjian; Jean Khoury; Pierre Laneuville; Richard Larson; Jeffrey Lipton; Joseph O. Moore; Tariq Mughal; Susan O'Brien; Javier Pinilla-Ibarz; Alfonso Quintas-Cardama; Jerald Radich; Vishnu Reddy; Charles Schiffer; Neil Shah; Paul Shami; Richard T. Silver; David Snyder; Richard Stone; Moshe Talpaz; Ayalew Tefferi; Richard A. Van Etten; Meir Wetzler.

Europe and Russia

Elisabetta Abruzzese; Jane Apperley; Massimo Breccia; Jenny Byrne; Francisco Cervantes; Ekaterina Chelysheva; R. E. Clark; Hugues de Lavallade; Iryna Dyagil; Carlo Gambacorti-Passerini;

John Goldman; Ibrahim Haznedaroglu; Henrik Hjorth-Hansen; Tessa Holyoake; Brian Huntly; Philipp le Coutre; Elza Lomaia; Francois-Xavier Mahon; David Marin-Costa; Giovanni Martinelli; Jiri Mayer; Dragana Milojkovic; Eduardo Olavarria; Kimmo Porkka; Johan Richter; Philippe Rousselot; Giuseppe Saglio; Guray Saydam; Jesper Stentoft; Anna Turkina; Paolo Vigneri; Andrey Zaritskey.

Latin America

Alvaro Aguayo; Manuel Ayala; Israel Bendit; Raquel Maria Bengio; Carlos Best; Eduardo Bullorsky; Eduardo Cervera; Carmino DeSouza; Ernesto Fanilla; David Gomez-Almaguer; Nelson Hamerschlak; Jose Lopez; Alicia Magarinos; Luis Meillon; Jorge Milone; Beatriz Moiraghi; Ricardo Pasquini; Carolina Pavlovsky; Guillermo J. Ruiz-Arguelles; Nelson Spector.

Australia and Asia

Christopher Arthur; Peter Browett; Andrew Grigg; Jianda Hu; Xiao-jun Huang; Tim Hughes; Qian Jiang; Saengsuree Jootar; Dong-Wook Kim; Hemant Malhotra; Pankaj Malhotra; Itaru Matsumura; Junia Melo; Kazunori Ohnishi; Ryuzo Ohno; Tapan Saikia; Anthony P. Schwarer; Naoto Takahashi; Constantine Tam; Tetsuzo Tauchi; Kensuke Usuki; Jianxiang Wang.

Middle East and Africa

Fawzi Abdel-Rahman; Mahmoud Deeb Saeed Aljurf; Ali Bazarbachi; Dina Ben Yehuda; Naeem Chaudhri; Muheez Durosinmi; Hossam Kamel; Vernon Louw; Bassam Francis Matti; Arnon Nagler; Pia Raanani; Ziad Salem.

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