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Price of drugs for chronic myeloid leukemia (CML), reflection of the unsustainable cancer drug prices: perspective of CML Experts

Experts in chronic myeloid leukemia

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The Price of Drugs for Chronic Myeloid Leukemia (CML); A Reflection of the Unsustainable Prices of Cancer Drugs: From the Perspective of a Large Group of CML Experts

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ABSTRACT

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, their impact on individual patients and healthcare policies, and argues for the need to lower the prices of cancer drugs to allow more patients to afford them and to maintain sound long-term healthcare policies.

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 save the vision of 30 million individuals), 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 two-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 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 about \$118,000 per year (1).

While cancer drug prices have been discussed recently by some financial analysts, and whenever new cancer drugs are approved, this Perspective reflects the views of a large group of CML experts, who believe the current prices of CML drugs are too high, unsustainable, may compromise access of needy patients to highly effective therapy, and are harmful to the sustainability of our national healthcare systems. These 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 \$5,000 per month to more than \$10,000 per month (2).

Innovation and discoveries must be rewarded. Pharmaceutical companies which invest in research and development and discover new life-saving drugs should benefit from healthy revenues. The cost for bringing a new cancer drug to market is reported to be about \$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 amongst 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 10-20% of that price (usually higher). This is what happened with imatinib,

priced in 2001 at \$2,200 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 endpoints, since most anti-cancer 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 about \$800,000 per year of increased survival (2). In many countries, an additional year lived is judged to be “worth” about \$50-100,000 (6, 7). In England, the National Institute for Health and Clinical Excellence (NICE) values a year lived at about 30,000 British pounds, or about \$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 about 5-6 years in the pre-imatinib era, a 50% improvement in survival would have extended life by 3 years, 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 \$2,200 per month, or \$26,000 per year (\$30,000 per year in the US) (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 US (the effect of imatinib on the prevalence of CML was then difficult to estimate), and full market penetration (i.e. most patients with CML receiving imatinib), the annual revenue from imatinib sales in the US would be about \$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%, versus a historical rate of 10-20%, and the estimated 10-year survival increased from less than 20% to above 80% (8). Patients with CML now live close to normal life spans (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 (US) where patients may pay an average of 20% of drug prices out-of-pocket (about \$20-30,000 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). This supports the notion that drug prices reflect geopolitical and socioeconomic dynamics unrelated to the cost of drug development. In the US, 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 anti-cancer 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 US, estimated at \$2.7 trillion in 2011, or 18% of the US GDP, compared with 6-9% in Europe (11). This increased expenditure does not add demonstrable benefit to US patients (12). 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 front-line allogeneic stem cell

transplantation, because it costs an average of \$30-80,000 dollars as a one-time procedure (13). This may harm patients because only a fraction may be eligible for transplantation (and may suffer from early mortality and life-long 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 yet unknown.

Imatinib was developed as a “goodwill gesture” by Novartis, and became a blockbuster, with annual revenues of about \$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 all research costs were accounted for in the original proposed price (5), that new indications were developed and FDA approved, and that the prevalence of the CML population continuing to take imatinib was dramatically increasing (14). This resulted in numerous appeals by patients and advocates to lower the price of imatinib, but to no avail so far (15, 16).

What determines a morally justifiable “just price” for 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 (17). 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 \$92-138,000 in the US, 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” (18). 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 US 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, its prevalence worldwide estimated today at about 1.2 -1.5 million patients. Based on sales, it is estimated that about 235,000-250,000 patients (less than 20-25%) are receiving imatinib. Support programs like the Glivec International Patient Assistance Program (GIPAP), a joint effort of Novartis and The Max Foundation, provides access to about 60,000 patients, about 30-40,000 of whom have CML (GIPAP providing TKIs to 1-3% of the world's CML population)(19). Thus, treatment penetration of TKIs in CML may be about 25-30% 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 above 80% (8,9,20). When treatment penetration may be lower, outcome may be worse. In the US, about 10% of patients fail to take prescribed drugs, largely because of cost (21). Trends

of CML survival in the US show an improvement since 2001, but the estimated 5-year survival rate is still around 60%, suggesting lower treatment penetration rates in the US compared with Sweden (20,22). Unaffordable drug prices in CML may be preventing many patients from accessing these life-saving 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 healthcare budget about \$1.1 trillion over 10 years (23). 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 healthcare system and patients. The Hatch Waxman Act provides a six-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 healthcare costs. Other generics can be marketed afterwards. 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 (report of the Federal Trade Commission on authorized generics, August, 2011) (24). 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 demand immediate attention, and which will need to consider many factors and involve many constituencies: FDA and governmental regulators; changes in legislation; patent laws; multitudes of regulatory agencies in the US and internationally; offices of human research protection (OHRP); impediments by lawyers and contract research organizations (CROs) 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 should also not exceed values that harm our patients and societies.

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Appendix

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Full appendix with conflicts of interest is available as an online supplement.

Table 1. Annual Price Estimates in thousands of US Dollars (rounded to nearest \$0.5 thousand), by Region, of Drugs Approved for the Treatment of Chronic Myeloid Leukemia

Country	Imatinib	Nilotinib	Dasatinib
US	\$92	115.5	123.5
Germany	54	60	90
UK	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 US from the RED Book Online (1) (accessed 2.20.2013).
- 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. (25). Prices of drugs in Germany may directly or indirectly influence drug prices in 31 countries (26).