

Lowering the High Cost of Cancer Drugs—I



To the Editor: In the August 2015 issue of *Mayo Clinic Proceedings*, the article by Tefferi et al¹ on the high cost of cancer drugs left many issues unaddressed or underaddressed.

First, the article could have questioned how the big pharmaceutical companies have always obtained drug prices that are not related to the true research and development costs, these costs being inferior to the marketing one.²

Second, the claim that “The good news is that effective new cancer therapies are being developed by pharmaceutical and biotechnology companies at a faster rate than ever before”¹ is far from evidence based. Easy-ride regulators are failing to compare new with current effective therapy using designs that are methodologically rigorous, and the use of surrogate end points replaces evidence with hope.^{3,4}

Drug prices are not related to their therapeutic value. This is a general issue, not specific to cancer drugs. Under current pricing, noninnovative “me-too” drugs are priced as high or higher than older drugs, without being more effective. The system has artificially increased the incentives for developing noninnovative me-too drugs rather than innovative medicines for unmet needs.⁵ As a result, in 2013, spending on specialty drugs, a category dominated by cancer drugs, totaled \$73 billion. That year, 8 new cancer drugs were approved by the US Food and Drug Administration. The Medicare price, which includes patient coinsurance, for these 8 drugs ranged from \$7000 to \$12,000 per month, with some agents producing overall survival improvement of nearly 6 months and others producing no improvement in overall survival.⁶

Last, the 30th World Oncology Forum convened by the European School of Oncology in 2012 with the task of evaluating progress to date in the war against cancer concluded that current strategies for controlling cancer are clearly not working. It issued a remarkable action plan that was concise: there were only 10 actions, with the war on tobacco being first.⁷

As Albert Einstein said, “Problems cannot be solved with the same mind set that created them.” We need innovative solutions if drug pricing is to become more appropriate and affordable.

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Lowering the High Cost of Cancer Drugs—II



To the Editor: We read with interest the article by Kantarjian and Rajkumar¹ in the April 2015 issue of *Mayo Clinic Proceedings* in which the

authors explored the main controversies surrounding the pricing of new innovative drugs, particularly drugs used in oncology and hepatology. Subsequently, in the August 2015 issue of the *Proceedings*, Tefferi and more than 100 cancer-specialist coauthors² addressed the same issue by emphasizing that cancer patients' out-of-pocket expenses have dramatically increased over the past few years and that these price increases are unsustainable.

Although different strategies to reduce drug prices and subsequently improve patients' adherence in using prescribed drugs were discussed in these 2 articles, one recent procurement tool—the price-volume agreement—was not mentioned by these authors, even though some experience has already accumulated with this tool, particularly in Europe.

In managing drug prices at the national level, price-volume agreements represent a procurement tool that markedly improves drug affordability by patients when the drug price is initially high but the treated patient population expands and becomes large. Specifically, these agreements determine a progressive price reduction as more and more patients are treated. Price reductions have generally been based on empirical data (eg, what is the cost of the recently introduced drug and how many patients are taking it?), but a theoretical basis for determining price may also be beneficial.³⁻⁵

We analyzed the price-volume agreement that the Italian Medicine Agency negotiated with the manufacturer of sofosbuvir, a nucleotide analogue drug used to manage hepatitis C virus infection. The price-volume agreement made in Italy is confidential,⁵ but some information has been reported in the media (the data presented herein are based on references from the Italian Medicine Agency website⁶ and from *Quotidiano La*

TABLE. Exponential Model for Handling Price-Volume Agreements^aEquation: $PRICE = f(Npt) = fPRICE e^{- (0.693/PHP) \times Npt}$

Where:

- Npt is the cumulative number of treated patients
- PRICE (in euro per patient) is the cost of the treatment (expressed as a function of Npt, which is assumed to undergo an exponential decay as Npt increases)
- fPRICE (in euro) is the “initial” price on the y-axis attributed to the treatment (ie, the full price with no discount)
- PHP (expressed as number of patients) is defined as the “price-halving population” and, in the framework of this exponential model, represents the number of patients at which the drug price is iteratively halved
- e is the base of the system of natural logarithms and equals approximately 2.718

^aThe equation describes the exponential model that relates a progressive price reduction to the increase in the number of treated patients.

Repubblica⁷). The Italian agreement with sofosbuvir’s manufacturer is very similar—in terms of parameterization and confidentiality—to the agreement introduced in France.⁸

In the absence of any recognized price-volume model, our analysis employed a simplified exponential equation reported in 2014.⁹ Our model (Table) includes the following information: (1) total number of patients who are candidates to receive the treatment; (2) number of patients actually treated; (3) treatment full price per patient (fPRICE); and (4) estimate of the nationwide budget impact in the absence of any price-volume intervention (calculated as fPRICE × number of patients actually treated). Although the decay is exponential, applying a logarithmic transformation to the y-axis data converts this curve into a straight line; hence, the knowledge of only 2 points permits one to determine a full model parameterization.

To estimate the model parameters ensuring the best fit to the “real decision” data made on sofosbuvir, we applied the 2-point linear interpolation with logarithmic transformation (using the following 2 data-pairs: price = 37,500 euro at $x = 0$ treated patients and price = 4000 euro at $x = 60,000$ treated patients).

The results of this 2-point fit were the following: fPRICE = 37,500 euro

per patient; price-halving population (expressed as number of patients) = 18,579 patients. The price of the drug tends therefore to be halved for every 18,579 treated patients, in an overall recruitment process involving a total of 60,000 patients. In addition, as a final parameter participating in the model, the nationwide budget impact in the absence of any price-volume intervention was easily estimated to be at 2.2 billion euro. (At an exchange rate of 1.091 US dollars per euro, 2.2 billion euro equals 2.4 US dollars.)

In the past, price-volume agreements have been applied on an empirical basis, ie, in the absence of any quantitative predetermined rule. The experience described herein for sofosbuvir is a first attempt that aims to generate a conceptual framework in this field. Interestingly enough, 3 parameters (price-halving population, fPRICE, and total number of patients who are candidates to receive the treatment) were found to ensure an adequate modeling of this price-volume relationship.

In handling the issue of drug pricing, critical cases similar to that involving sofosbuvir are likely to occur quite frequently, especially in areas of pharmacotherapy such as oncology and cardiovascular-targeted drugs (eg, evolocumab¹⁰). In this context, the availability of a rational model is a useful prerequisite to ensure that

price-volume decisions made for different agents are not purely empirical but tend to share the same rationale or the same operational strategy.

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Lowering the High Cost of Cancer Drugs—III



To the Editor: In their commentary published in the August 2015 issue of *Mayo Clinic Proceedings*, Tefferi et al¹ correctly argue that new cancer medicines in the United States are priced above international norms, at times prohibitively so. However, their recommendation that patients import cancer medicines for “personal use,” while pointing out that “prices in Canada are about half of prices in the United States,” is so fraught with danger as to be foolish.

Canada has cheaper new cancer medicines because federal law regulates the prices of patented drugs (although generic drugs are often more expensive).^{2,3} American patients can buy drugs at lower Canadian prices by crossing the border, but it is usually easier to order from Canadian Internet pharmacies.

The trouble is, most “Canadian” Internet pharmacies are anything but. The US Food and Drug Administration (FDA) reports that 85% of medicines purchased from “Canadian” Internet pharmacies are actually foreign frauds, “falsely promoted as being of Canadian

origin”.⁴ Investigations by an Internet security company found foreign organized criminals masquerading as Canadian pharmacists and using fake pharmacy licenses.⁵

Further, even Internet pharmacies on Canadian soil that advertise medicines to Americans do so illegally. The worst are not licensed pharmacies at all but just call centers, while others are licensed pharmacies that advertise medicines from countries such as India or Turkey whose safety has never been scrutinized or approved by either Health Canada or the FDA.⁶ Touting these unapproved medicines, Health Canada writes, “is a violation of the *Food and Drugs Act* and *Food and Drug Regulations*.”⁷ As the commissioner of the FDA has warned, when the unapproved medicines arrive in the United States, that violates American law as well.⁸

The danger of unapproved medicines is obvious. A prominent licensed Canadian Internet pharmacy, CanadaDrugs.com, and its associates advertised and sold discounted versions of the expensive anticancer medication bevacizumab (Avastin) directly to American physicians. The product that arrived came from Turkey and was fake: it contained no active ingredient.⁹⁻¹¹ CanadaDrugs.com and its associates have now been indicted by the US Department of Justice for criminal activities including conspiracy to smuggle and money laundering.¹² In addition to Canadadrugs.com, several people, including physicians, have been and still are being prosecuted for the importation and sale of counterfeit Avastin in the United States, and some have gone to prison.¹²

Shamefully, Canada’s government encourages this sort of organized crime: Parliament even voted to not enforce the law against Internet pharmacies.⁶ Accordingly, in subsequent criminal investigations by the Royal Canadian Mounted Police, no one was prosecuted.⁶

However, the biggest problem of recommending that American cancer patients obtain medicine from Canada—a country having about one-tenth the population of the United States—is that it would drain Canada’s much smaller supply of drugs and assuredly cause drug shortages for Canadian cancer patients. Oncology practice suffers from drug shortages already.¹³ For Tefferi et al¹ and others to advocate that their American patients parasitize Canada’s limited drug supply not only threatens to make that worse but is also appallingly unethical because it amounts to redistributing scarce, life-saving resources to Americans at the expense of Canadian cancer patients’ lives—in violation of the rule of distributive justice in medical ethics.¹⁴ Simply put, good neighbors do not raid one another’s medicine chest. That is not only unethical advice but could also land American doctors in prison if they play a part in importing medicines illegally.

Obviously, America needs home-grown solutions to its drug access challenges. Regardless of the form that takes, advocates must remember that it is the responsibility of elected representatives in Washington, and not foreigners in Ottawa, to provide what Americans need.

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