Commentary

Are High Drug Prices for Hematologic Malignancies Justified? A Critical Analysis

Jagpreet Chhatwal, PhD[1]; Michael Mathisen, PharmD[2]; and Hagop Kantarjian, MD[3]

In the past 15 years, treatment outcomes for hematologic malignancies have improved substantially. However, drug prices have also increased drastically. This commentary examines the value of the treatment of hematologic malignancies at current prices in the United States through a reanalysis of a systematic review evaluating 29 studies of 9 treatments for 4 hematologic malignancies. Incremental cost-effectiveness ratios (ICERs) were calculated on the basis of drug prices in the United States in 2014. Sixty-three percent of the studies (15 of 24) had ICERs higher than $50,000 per quality-adjusted life-year (QALY), the benchmark widely used by health economists to define cost-effectiveness. In studies evaluating the current standard-of-care treatments for chronic myeloid leukemia, the ICERs for tyrosine kinase inhibitors versus hydroxyurea or interferon ranged from $210,000 to $426,000/QALY. The lower ICER values were mostly obtained from 11 studies evaluating rituximab, which was approved by the Food and Drug Administration in 1997 (ICER range, $37,000-$69,000/QALY). In conclusion, the costs of the majority of new treatments for hematologic cancers are too high to be deemed cost-effective in the United States. ***Cancer* 2015;121:3372-9.** © *2015 American Cancer Society.*

KEYWORDS: critical analysis, drug, hematologic malignancies, high, prices.

INTRODUCTION

Over the past 15 years, cancer drug prices have risen drastically. The average price of a cancer drug was $5000 to $10,000 before 2000 and increased to more than $100,000 in 2012.[1,2] In that year, 12 of the 13 drugs approved by the Food and Drug Administration for cancer indications were priced higher than $100,000. In 2014, almost every new cancer drug approved had a price range between $120,000 and $170,000.

During the same period, the average household income decreased approximately 8% to a median of $52,000.[3] Recent trends in insurance coverage have shifted a significant burden of the cost of care to patients, with out-of-pocket expenses of approximately 20% to 30% for specialty drugs.[4] Cancer is estimated to affect 1 in 3 individuals in their lifetime. Many individuals and families will thus face a common, potentially catastrophic situation of a cancer diagnosis within the family and the need for a cancer treatment, for which the out-of-pocket expense will be approximately $25,000 to 30,000, more than half the average household income. This is more significant for senior citizens, who are disproportionately more affected by cancer and have a lower average income.[5]

Advances in the understanding of cancer pathophysiologies and in therapies have improved the prognosis for many cancers and particularly for hematologic malignancies such as acute leukemia, chronic leukemia, lymphoma, and multiple myeloma. However, medical experts have questioned the value of these drugs at their current high prices.[6] In a recent systematic review, Saret et al[7] assessed the value of innovation in hematologic malignancies by identifying 29 studies published from 1996 to 2012 with the Tufts Medical Center CEA Registry (https://research.tufts-nemc.org/cear4/). These included 9 treatments (interferon-α, alemtuzumab, bendamustine, thalidomide, lenalidomide, bortezomib, dasatinib, imatinib, and rituximab) for 4 hematologic cancers: chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma, and multiple myeloma. The authors concluded that innovative treatments for hematologic malignancies provide reasonable value for the money in the United States.

Corresponding author: Hagop Kantarjian, MD, Department of Leukemia, The University of Texas MD Anderson Cancer Center, 1400 Holcombe Boulevard, Unit 428, Houston, TX 77030; hkantarjian@mdanderson.org

[1]Department of Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, Texas; [2]Epocrates Medical Information, AthenaHealth, San Francisco, California; [3]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas

Michael Mathisen was formerly affiliated with the Departments of Pharmacy and Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX.

All authors contributed to the concept and design, the analysis and interpretation of data, and the drafting of the article.

The views in this article are in not in any way affiliated with AthenaHealth or Epocrates.

DOI: 10.1002/cncr.29512, **Received:** May 1, 2015; **Revised:** May 18, 2015; **Accepted:** May 19, 2015, **Published online** June 23, 2015 in Wiley Online Library (wileyonlinelibrary.com)

The analysis was based on the costs of the drugs in past years, which were substantially lower than the current prices, on studies conducted within and outside the United States, and on a combination of heterogeneous cost-effectiveness analyses of different hematologic cancers. Our objective was to update the outcomes of the 29 cost-effectiveness studies through the use of current drug costs and revisit the conclusions.

HOW IS TREATMENT VALUE ANALYZED?

We first describe cost-effectiveness analysis, a commonly used approach to assess the value of a treatment. Cost-effectiveness analysis assesses the incremental benefits and costs of an intervention in comparison with the old or existing intervention. A special case of cost-effectiveness analysis is cost-utility analysis, in which the health benefits (ie, effects) are typically measured in terms of quality-adjusted life-years (QALYs).[8,9] Because these measures were used in the analysis by Saret et al[7] and are critical to understanding the results and conclusions, we detail them next in simple terms.

QALY determines both the quality and quantity of life lived. The quality of life is typically determined by health state weights, where 1 represents perfect health and 0 represents death. For example, 5 years lived in a perfectly health state will be counted as 5 QALYs (ie, 5×1.0), whereas 5 years lived in a morbid condition with a 50% reduction in a patient's quality of life will result in 2.5 QALYs (ie, 5×0.5).

Cost-effectiveness is typically expressed as an incremental cost-effectiveness ratio (ICER), the ratio of the change in costs to the change in effects (eg, QALYs). For example, consider existing drug A, which results in total costs of $50,000 (which includes the costs of managing adverse events) over a patient's lifetime and in a total of 8.5 QALYs. Suppose new drug B, which costs more and improves survival, becomes available. The use of drug B results in total costs of $100,000 and 10.5 QALYs. The ICER of drug B is calculated as the ratio of $50,000 (ie, $100,000 – $50,000) to 2.0 (ie, 10.5 – 8.5), which is equal to $25,000. The ICER value is used to determine whether a new intervention is cost-effective in comparison with an existing one. The ICER tells how much more is spent to gain 1 additional QALY (in this case, $25,000/QALY).

Most developed countries consider a well-defined willingness-to-pay threshold, which indicates how much of a maximum price a payer is willing to pay to gain an additional QALY. If the ICER of an intervention is below the willingness-to-pay threshold, the intervention is deemed cost-effective; that is, it provides a good value for the money. For example, the United Kingdom typically uses £30,000/QALY, and Canada uses $50,000/QALY.[10] Although no such threshold exists in the United States, the majority of the published studies use $50,000/QALY. Therefore, with the aforementioned metric, we can conclude that drug B is cost-effective in comparison with drug A, and additional resources spent on drug B provide a good value for the money.

REANALYSIS OF COST-EFFECTIVENESS STUDIES

Saret et al[7] evaluated the 29 studies listed in Table 1.[11-39] They addressed the cost-effectiveness of drugs approved between 1986 and 2006 (median year of Food and Drug Administration approval, 2001) in studies published between 1995 and 2012 (median year of publication, 2006). Notably, 21 of the 29 analyzed studies (72%) were industry-funded; 24 of 29 (83%) were conducted before 2011; and 18 of the 29 studies (62%) were conducted outside the United States (United Kingdom, Canada, France, Sweden, the Netherlands, and Norway) and used the price of drugs in the year of the study in the particular geographic area.[7]

The primary concern with the analysis[7] is the price of the treatment used to measure cost-effectiveness and reach conclusions. In the analysis, the authors did not adjust for the updated drug costs from the year of the original modeling study. For example, the ICER related to imatinib from the studies published in 2001 and 2005 was based on the price of imatinib in the United States in 2001 ($26,000 per year of therapy) and the price of imatinib in the United Kingdom in 2005 ($50,000 per year of therapy). However, the price of imatinib in 2014 was $132,000 per year of therapy (average wholesale price from *RED BOOK* [accessed January 15, 2015]). The drug prices from past years should not be used to justify cancer drug prices in 2014.

Second, the price of the drug from countries outside the United States was used to justify a reasonable treatment value in the United States. The prices of cancer drugs are 20% to 70% lower in Canada and European countries in comparison with the United States (Table 2).[40] Eighteen of the 29 studies were performed outside the United States. Non-US cost-effectiveness analyses may not reflect cancer drug prices in the United States.

In our analysis, we updated the ICERs of these studies by using the US drug prices in 2014. We excluded 9 studies[31-39] for the following reasons: 1) 3 studies compared interferon-α with hydroxyurea or the addition of

TABLE 1. Details of the 29 Studies Analyzed to Measure the Cost-Effectiveness of Treatment for Hematologic Malignancies

Source	Indication	Drug Price Year	Sponsor	Drug Intervention	Reported ICER	ICER Adjusted With Drug Prices in 2014
Dalziel 2005[11]	CML frontline therapy	2002	UK NHS	IM vs IFN	$44,270	$274,743
				IM vs hydroxyurea	$44,270	$426,260
Ghatnekar 2010 [12]	CML resistant to imatinib	2008	Bristol-Myers Squibb	DASA vs IM[a]	$9577	($803,067)[b]
				DASA vs IM	$9577	$210,778
Reed 2004[13]	CML frontline therapy	2002	Novartis	IM vs INF + ara-C	$43,300	$329,428
Reed 2008[14]	CML	2006	Novartis	IM vs INF + ara-C	$53,868	$220,620
Warren 2004[15]	CML second-line therapy	2001	Novartis	IM vs hydroxyurea after IFN failure	$55,817	$308,626
Gordois 2003[16]	Advanced CML	2001	Novartis	Accelerated; IM vs DAT	$42,578	$229,320
				Blast, IM vs DAT	$61,289	$243,082
Hornberger 2010[17]	RR-MM	2010	Johnson & Johnson	BORT vs DEX	$125,748	$139,160
				BORT vs LEN-DEX	Cost-saving	($1,746,305)[b]
Moller 2011[18]	RR-MM	2010[c]	Celgene	LEN-DEX vs BORT	$42,776	$37,605
Hornberger 2004[19]	DLBCL	2003[c]	Genentech	R-CHOP vs CHOP	$19,297	$45,485
Johnston 2010[20]	DLBCL	2006	Foundation	R-CHOP vs CHOP	$19,144	$69,310
Best 2005[21]	DLBCL	2003	Roche	R-CHOP vs CHOP	$14,956	$41,487
Groot 2005[22]	DLBCL	2003	None	R-CHOP vs CHOP	$21,878	$60,434
Deconinck 2010[23]	RR-FL	2006	Roche	R vs observation	$11,514	$51,778
Hayslip 2008[24]	FL	2006		R after second remission vs observation	$19,522	$406,282
Hornberger 2012[25]	FL	2011	Genentech	R maintenance vs observation	$34,842	$55,350
Hornberger 2008[26]	Advanced FL	2006	Genentech	R-CVP vs CVP in advanced follicular NHL	$28,565	$50,037
Kasteng 2008[27]	FL	2007	Roche	R maintenance after second-line therapy	$17,240	$37,354
Ray 2010[28]	FL (first-line)	2008	Roche	R-CHOP vs CHOP	$15,833	$42,170[d]
Hornberger 2012[29]	Untreated CLL	2011	Genentech	FC vs FCR	$31,513	$43,808
Woods 2012[30]	CLL	2009	Napp Pharmaceuticals	BEND vs CHL	$19,339	$20,938[e]
Beck 2001[31]	CML	2000	Schering Plough	IFN + ara-C	$17,380	N/A
Kattan 1996[32]	CML	1995	NIH	IFN vs hydroxyurea	$81,500	N/A
Liberato 1997[33]	CML		Italian Government			N/A
Gulbrandsen 2001[34]	MM	2000	Norwegian Cancer Society	Auto-SCT		N/A
Nord 1997[35]	MM	1995	Schering-Plough	IFN-MP vs MP	$110,000	N/A
Scott & Scott 2007[36]	CLL		Bayer			N/A
Wirt 2001[37]	FL		Schering-Plough			N/A
Soini 2011[38]	FL	2008	Roche	R-CHOP-R vs R-CHOP vs CHOP		N/A[d]
Doss 2011[39]	Health technology assessment summary					N/A

Abbreviations: ara-C, cytosine arabinoside; auto-SCT, autologous stem cell transplantation; BEND, bendamustine; BORT, bortezomib; CHL, chlorambucil; CHOP, cyclophosphamide, adriamycin, vincristine, and prednisolone; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CVP, cyclophosphamide, vincristine, prednisone; DASA, dasatinib; DAT, daunorubicin, cytosine arabinoside, and 6-thioguanine; DEX, dexamethasone; DLBCL, diffuse large B cell lymphoma; FC, fludarabine and cyclophosphamide; FCR, fludarabine, cyclophosphamide, and rituximab; FL, follicular lymphoma; ICER, incremental cost-effectiveness ratio; IFN, interferon-α; IM, imatinib; LEN, lenalidomide; MM, multiple myeloma; MP, melphalan; N/A, not available; NHL, non-Hodgkin lymphoma; NHS, National Health Services; NIH, National Institutes of Health; R, retuximab; RR-FL, relapsed refractory follicular lymphoma; RR-MM, relapsed refractory multiple myeloma.

[a] Comparison of DASA and IM at 400 mg twice daily.

[b] Cost-saving.

[c] All costs are based on the year preceding the year of study publication.

[d] Only R-CHOP versus CHOP was considered.

[e] New drug prices were used for both drugs.

[f] This could not be calculated because the sensitivity analysis was based on the ICER and the cost of the drug.

cytarabine to interferon for CML[31-33] (these were not used in CML therapy in 2014; 2) 1 study in 1997 evaluated the addition of interferon for the treatment of myeloma[35] (this was not the standard of care in 2014); 3) 2 studies of lymphoma did not have the data needed to calculate ICERs in 2014[37,38]; 4) 1 study evaluated alemtuzumab for CLL[36] (alemtuzumab was withdrawn from the market and reintroduced under a different label to treat multiple sclerosis); 5) 1 study evaluated autologous stem cell transplantation for multiple myeloma[34] (not drug therapy); and 6) 1 study was a UK guidance on thalidomide and bortezomib in myeloma that did not provide

TABLE 2. Comparison of Prices of Some Antineoplastic Agents Used for Hematologic Malignancies

Parenteral Drug (US Brand Name)	US Indication	Dose	Monthly or Per-Cycle Cost (US Dollars Rounded to Nearest $100)			Cost: Canada/UK vs US (%)
			US	Canada	UK	
Brentuximab vedotin (Adcetris)	Hodgkin lymphoma	1.8 mg/kg every 3 wk	$20,300	$12,800	$11,500	57-63
Obinutuzumab (Gazyva)	CLL	1000 mg every 4 wk	$6200	$4700	$5100	76-82
Oral Drug (US Brand Name)	**US Indication**	**Dose**	**Yearly Cost (US Dollars Rounded to Nearest $500)**			**Cost: Canada/UK vs US (%)**
			US	Canada	UK	
Bosutinib (Bosulif)	CML	500 mg daily	$143,500	$48,000	$64,000	33-45
Imatinib (Gleevec)	CML	400 mg daily	$132,500	$38,000	$32,000	24-29
Imatinib (generic)	CML	400 mg daily	N/A	$8820	N/A	-
Nilotinib (Tasigna)	CML	300 mg twice daily	$131,500	$37,000	$45,000	28-34
Dasatinib (Sprycel)	CML	100 mg daily	$138,500	$52,000	$47,000	34-38
Ibrutinib (Imbruvica)	CLL	420 mg daily	$126,500	$79,000	$84,500	62-67
Lenalidomide (Revlimid)	Multiple myeloma	25 mg daily (21 of 28 d)	$142,000	$96,500	$80,500	55-68

Abbreviations: CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; N/A, not available; US, United States; UK, United Kingdom.
This table was adapted from *JAMA Oncology*.[40]

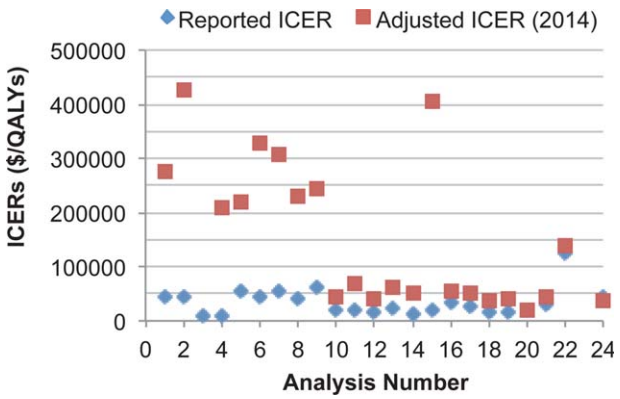

Figure 1. Comparison of ICERs before and after adjustments for drug prices in the United States in 2014. The analysis numbers on the x-axis refer to the order in which the studies are listed in Table 1. ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

details for recalculating the ICER in 2014.[39] We were left with 20 studies and 24 cost-effectiveness analyses.

We updated the ICERs of each study by 1 of 2 methods. With the first method, we updated the ICERs with the reported sensitivity analysis of drug costs in the original cost-effectiveness study. For example, if the original study reported ICERs at lower and upper values of drug costs, we used the linear relation between ICERs and drug costs to find the updated ICER at 2014 drug costs. Alternatively, we updated the reported total cost of treatment from the published decision analytic model with 2014 drug costs and recalculated the ICERs. We converted non-US currencies to US dollars with the historic exchange rates appropriate for each study. Finally, we updated all costs to 2014 with the Consumer Price Index.[41]

Table 1 shows the reported ICERs and the recalculated ICERs in dollars per QALY as the real treatment values in 2014. As shown in Figure 1, the ICERs (dollars per QALY) in 2014 were mostly several-fold higher than those calculated in the original studies. For example, in the 5 CML studies, the ICER values for tyrosine kinase inhibitors versus hydroxyurea or interferon ranged from $210,000 to $426,000/QALY and exceeded the commonly used willingness-to-pay threshold of $50,000/QALY. The only exception was the comparison of dasatinib with imatinib (800 mg daily) for CML salvage, but the comparator was an artificially expensive one (double the standard dose of imatinib) that is not considered a reasonable treatment by some CML experts. Figure 2 shows that 63% (15 of 24) of the studies had ICERs higher than $50,000/QALY. Most of the lower ICER values were from 11 of the 20 studies analyzing rituximab, a monoclonal antibody that was approved by the Food and Drug Administration in 1997 (18 years ago) and that is expected to have a historically low established price and consequently a lower ICER value.

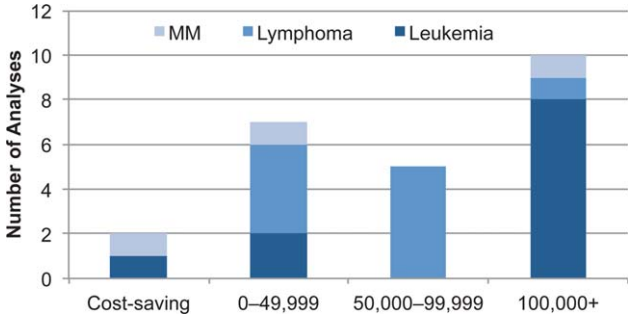

Figure 2. Incremental cost-effectiveness ratios by cancer type and range in 2014 US dollars. MM indicates multiple myeloma.

We also carefully scrutinized the potential bias related to industry-funded studies. Two industry-sponsored studies compared bortezomib with lenalidomide plus dexamethasone or with dexamethasone alone.[17,18] The 2 analyses used data from the same multi-institutional studies. The first, sponsored by Johnson & Johnson (the bortezomib drug company), concluded that bortezomib provided a good treatment value in comparison with lenalidomide plus dexamethasone (although not in comparison with dexamethasone alone, the actual standard of care). In contrast, using the same clinical data, the second analysis, sponsored by Celgene (the lenalidomide drug company), reached the conclusion that lenalidomide/dexamethasone provided a good treatment value in comparison with bortezomib. On the basis of the provided data, we could not calculate the ICER for lenalidomide versus dexamethasone. This highlights the fact that industry-funded studies may have a significant bias related to the choice of the study design, selection of comparators, methodology, and clinical assumptions.[42]

In their analysis,[7] Saret et al. combined the results of 29 studies and presented a median ICER. Their simplified approach ignored the heterogeneity in underlying disease progression, patient characteristics, modeling assumptions, and so forth. For example, operator-dependent assumptions such as health-related quality-of-life of the model states (eg, 0.6 vs 0.8) can influence QALYs and ICERs drastically. Similarly, the choice of comparators in the cost-effectiveness analysis is an important factor (eg, comparing tyrosine kinase inhibitors with hydroxyurea or interferon or comparing dasatinib with imatinib at 400 or 800 mg daily). In contrast to meta-analyses of clinical trials and observational studies, no standards exist for combining cost-effectiveness results in a systematic way. Therefore, a conclusion based on a median ICER of studies that does not account for heterogeneous factors could be misleading. The median ICER value could be perceived to be lower if the analysis included many studies of a lower priced drug (rituximab in this case: 11 of the 20 evaluable studies). If newer therapies are considered (eg, tyrosine kinase inhibitors for CML, lenalidomide/bortezomib for myeloma, B-cell receptors inhibitors for CLL, and checkpoint inhibitors), then all the individual ICER values but one far exceed the accepted $50,000/QALY (Table 1). Several recently published studies of newer treatments for hematologic cancers reflect the high prices of such novel treatments.[43-46]

DISCUSSION

Saret et al[7] concluded that "innovative treatments for hematologic malignancies may provide reasonable value for money." The authors cautioned that their analysis included a limited number of studies, some older drugs, and a mixture of industry-funded and non–industry-funded studies. In further discussions, they clarified that the cost-effectiveness ratios may have changed over time because of the increase in drug prices. Despite these caveats, the study was interpreted in several medical news outlets to support the notion that high drug prices for hematologic malignancies are justified because they offer high treatment value.[47,48] Because the analysis used the older drug prices in the particular year and geographic area of each study, the conclusions may not justify the high current cancer drug prices in the United States today.

Our analysis accounted for these issues and reached different conclusions: the current prices of the majority of the drugs used to treat hematologic malignancies are not justified. The estimated ICERs (dollars per QALY) of most studies published until 2012 far exceeded a good treatment value. Our conclusions are different because we used the current drug prices and accounted for the price differences between the United States and elsewhere. With today's costs, the drug prices far exceed their treatment values and should, therefore, be scrutinized.

We agree that the debates in health care costs should consider the value of breakthrough drugs, not just the costs. With the metric commonly used in health economics, the high drug prices are not justified. It is worth noting that the studies on which the analysis of Saret et al[7] and our re-analysis were based did not include any new drugs or studies after 2012. Our search identified several recent studies in which the ICERs of drugs far exceeded the commonly accepted willingness-to-pay threshold of

$50,000/QALY,[43-46] and this is in line with our conclusions.

The reasons behind the significant rise in cancer drug prices may be traced to the Medicare Reform Act of 2003, in which legislation was inserted that prevented Medicare from negotiating drug prices, and to the added legislation of Medicare Part D, which requires Medicare to pay for all such oral drugs.[49] This left drug companies as the sole decision makers on how high to price a novel treatment or how much to increase the annual price of older therapies. This situation translated into significant increases in drug company revenues since 2006 when the legislature was implemented.[50] A study by Howard et al[51] showed that cancer drug prices have increased by an average of $8500 per year over the past 15 years, and the initial drug price in the United States serves as the starting bargaining point for insurance companies in the United States and for health care entities outside the United States. The same study reported that the cost of drugs for each additional year lived, after adjustments for inflation, increased from $54,000 in 1995 to $207,000 in 2013. Therefore, regulations on the cost of new treatments, as commonly performed in almost all other developed countries, will make health care more affordable for patients and providers in the United States.

High drug costs also have direct implications for patients. Studies have shown that 10% to 20% of patients cannot afford the treatments and decide either not to take them or to compromise them.[52,53] Patients are faced with the hard choice of using their financial resources to prolong their lives or foregoing the treatment to save money for other family necessities (food, education, and housing). With the ever rising cost of cancer treatment, we could soon reach a point at which our health care system can no longer timely treat all patients with cancer, as is currently the case with hepatitis C drugs.[54]

In our analysis, which disregarded drugs of little or no use today (interferon-α and alemtuzumab), the drugs offering good treatment value were rituximab and bendamustine. Rituximab was approved by the Food and Drug Administration in 1997 (18 years ago) and is expected to be even less expensive today. Still, its ICER ranged from $37,000 to $69,000/QALY (with 1 high exception of $406,000/QALY). Bendamustine, an alkylating agent available in East Germany since the 1950s and revitalized for the treatment of lymphoid malignancies, showed a reasonable treatment value. This left in the analysis only the tyrosine kinase inhibitors for the treatment of CML and the 2 myeloma drugs lenalidomide and bortezomib, all of which were calculated to have high ICERs in comparison with the older standard of care. A recent wave of new and promising drugs for hematologic malignancies is of concern because of their high prices, which were not considered in the current analysis. These include the new tyrosine kinase inhibitors (bosutinib and ponatinib) and omacetaxine for CML, the new B cell receptor inhibitors for CLL and lymphoma (ibrutinib and idelalisib), the new monoclonal antibodies for lymphoid malignancies (ofatumumab, obinutuzumab, and blinatumomab), the new-generation immunomodulatory inhibitory derivatives and proteasome inhibitors for myeloma, and the new checkpoint inhibitors.

An issue with economic analyses (unrelated to this study) is the operative-dependent assumptions, which can be subjective and depend on the particular investigators' interests. Modeling and data assumptions can vary significantly. These include the value assigned to quality of life in a particular year of life, the price and duration of an intervention, the price of complications of an intervention (eg, related to hospitalization), the price and need of additional interventions caused by these complications, and other factors. For example, the morbidity factor for a year lived can be valued as 0.6 or 0.8 according to subjective assumptions, and this would make a drastic difference in the calculated ICER value. This highlights the issue of whether these measures could be standardized more objectively.

Borrowing from the experience in human immunodeficiency virus and acquired immune deficiency syndrome, we realize that such patients can now live a normal life span but require daily therapy with drugs that cost $10,000 to 18,000 per year. In essence, patients with acquired immune deficiency syndrome pay less than $20,000 per year lived. Many new therapies for cancer are following the trend of daily oral therapies for a lifetime.[55] However, in cancer, therapies have staggering costs of more than $120,000 per year lived; this is an expensive endeavor not affordable by many patients with cancer, including the well-insured. Efforts should continue to develop cancer policies that make cancer therapies available and affordable to all. Cancer drugs with lower prices will have significantly better and stable market penetration, and this will allow many more patients to live longer on therapies and thus increase longer term drug company profits.[56] In essence, drug companies will do good and do well.

FUNDING SUPPORT

No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURES

Jagpreet Chhatwal has received consulting fees from Gilead Sciences for an unrelated project and reports personal fees from Merck, Novosys, and Complete HEOR Solutions outside the submitted work. Hagop Kantarjian is a Scholar in Health Policy at the Baker Institute and a member of the American Society of Clinical Oncology board of directors; he has received research grants from Novartis, Bristol-Myers Squibb, ARIAD, and Pfizer.

REFERENCES

1. Kantarjian H, Steensma D, Rius Sanjuan J, Elshaug A, Light D. High cancer drug prices in the United States: reasons and proposed solutions. *J Oncol Pract*. 2014;10:e208-e211.
2. Kantarjian H, Rajkumar SV. Why are cancer drugs so expensive in the United States, and what are the solutions? *Mayo Clinic Proc*. 2015;90:500-504.
3. US Census Bureau. Income and poverty in the United States. http://www.census.gov/content/dam/Census/library/publications/2014/demo/p60-249.pdf. Published September 2014. Accessed April 28, 2015.
4. Henry J. Kaiser Family Foundation. How much "skin in the game" is enough? The financial burden of health spending for people on Medicare. An updated analysis of out-of-pocket spending as a share of income. http://kaiserfamilyfoundation.files.wordpress.com/2013/01/8170.pdf. Accessed January 15, 2015.
5. Henry J. Kaiser Family Foundation. Medicare at a glance. http://kff.org/medicare/fact-sheet/medicare-at-a-glance-fact-sheet/. Published September 2, 2014. Accessed March 16, 2015.
6. Experts in Chronic Myeloid Leukemia. 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. *Blood*. 2013;121:4439-4444.
7. Saret CJ, Winn A, Shah G, et al. Value of innovation in hematologic malignancies: a systematic review of published cost-effectiveness analyses. *Blood*. 2015;125:1866-1869.
8. Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. *JAMA*. 1996;276:1172-1177.
9. Petitti DB. Meta-Analysis, Decision Analysis and Cost-Effectiveness Analysis: Methods for Quantitative Synthesis in Medicine. Oxford, England: Oxford University Press; 1994.
10. National Institute for Health and Care Excellence. The appraisal of the evidence and structured decision-making. https://www.nice.org.uk/article/pmg9/chapter/6-the-appraisal-of-the-evidence-and-structured-decision-making. Published April 2013. Accessed March 18, 2015.
11. Dalziel K, Round A, Garside R, et al. Cost effectiveness of imatinib compared with interferon-alpha or hydroxycarbamide for first-line treatment of chronic myeloid leukaemia. *Pharmacoeconomics*. 2005;23:515-526.
12. Ghatnekar O, Hjalte F, Taylor M. Cost-effectiveness of dasatinib versus high-dose imatinib in patients with Chronic Myeloid Leukemia (CML), resistant to standard dose imatinib—a Swedish model application. *Acta Oncol*. 2010;49:851-858.
13. Reed SD, Anstrom KJ, Ludmer JA, et al. Cost-effectiveness of imatinib versus interferon-alpha plus low-dose cytarabine for patients with newly diagnosed chronic-phase chronic myeloid leukemia. *Cancer*. 2004;101:2574-2583.
14. Reed SD, Anstrom KJ, Li Y, et al. Updated estimates of survival and cost effectiveness for imatinib versus interferon-alpha plus low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukaemia. *Pharmacoeconomics*. 2008;26:435-446.
15. Warren E, Ward S, Gordois A, et al. Cost-utility analysis of imatinib mesylate for the treatment of chronic myelogenous leukemia in the chronic phase. *Clin Ther*. 2004;26:1924-1933.
16. Gordois A, Scuffham P, Warren E, et al. Cost-utility analysis of imatinib mesilate for the treatment of advanced stage chronic myeloid leukaemia. *Br J Cancer*. 2003;89:634-640.
17. Hornberger J, Rickert J, Dhawan R, et al. The cost-effectiveness of bortezomib in relapsed/refractory multiple myeloma: Swedish perspective. *Eur J Haematol*. 2010;85:484-491.
18. Moller J, Nicklasson L, Murthy A. Cost-effectiveness of novel relapsed-refractory multiple myeloma therapies in Norway: lenalidomide plus dexamethasone vs bortezomib. *J Med Econ*. 2011;14:690-697.
19. Hornberger JC, Best JH. Cost utility in the United States of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone for the treatment of elderly patients with diffuse large B-cell lymphoma. *Cancer*. 2005;103:1644-1651.
20. Johnston KM, Marra CA, Connors JM, et al. Cost-effectiveness of the addition of rituximab to CHOP chemotherapy in first-line treatment for diffuse large B-cell lymphoma in a population-based observational cohort in British Columbia, Canada. *Value Health*. 2010;13:703-711.
21. Best JH, Hornberger J, Proctor SJ, et al. Cost-effectiveness analysis of rituximab combined with chop for treatment of diffuse large B-cell lymphoma. *Value Health*. 2005;8:462-470.
22. Groot MT, Lugtenburg PJ, Hornberger J, et al. Cost-effectiveness of rituximab (MabThera) in diffuse large B-cell lymphoma in the Netherlands. *Eur J Haematol*. 2005;74:194-202.
23. Deconinck E, Miadi-Fargier H, Pen CL, et al. Cost effectiveness of rituximab maintenance therapy in follicular lymphoma: long-term economic evaluation. *Pharmacoeconomics*. 2010;28:35-46.
24. Hayslip JW, Simpson KN. Cost-effectiveness of extended adjuvant rituximab for US patients aged 65-70 years with follicular lymphoma in second remission. *Clin Lymphoma Myeloma*. 2008;8:166-170.
25. Hornberger J, Chien R, Friedmann M, et al. Cost-effectiveness of rituximab as maintenance therapy in patients with follicular non-Hodgkin lymphoma after responding to first-line rituximab plus chemotherapy. *Leuk Lymphoma*. 2012;53:2371-2377.
26. Hornberger J, Reyes C, Lubeck D, et al. Economic evaluation of rituximab plus cyclophosphamide, vincristine and prednisolone for advanced follicular lymphoma. *Leuk Lymphoma*. 2008;49:227-236.
27. Kasteng F, Erlanson M, Hagberg H, et al. Cost-effectiveness of maintenance rituximab treatment after second line therapy in patients with follicular lymphoma in Sweden. *Acta Oncol*. 2008;47:1029-1036.
28. Ray JA, Carr E, Lewis G, et al. An evaluation of the cost-effectiveness of rituximab in combination with chemotherapy for the first-line treatment of follicular non-Hodgkin's lymphoma in the UK. *Value Health*. 2010;13:346-357.
29. Hornberger J, Reyes C, Shewade A, et al. Cost-effectiveness of adding rituximab to fludarabine and cyclophosphamide for the treatment of previously untreated chronic lymphocytic leukemia. *Leuk Lymphoma*. 2012;53:225-234.
30. Woods B, Hawkins N, Dunlop W, et al. Bendamustine versus chlorambucil for the first-line treatment of chronic lymphocytic leukemia in England and Wales: a cost-utility analysis. *Value Health*. 2012;15:759-770.
31. Beck JR, Guilhot J, Giles FJ, et al. Cytarabine added to interferon improves the cost-effectiveness of initial therapy for patients with early chronic phase chronic myelogenous leukemia. *Leuk Lymphoma*. 2001;41:117-124.
32. Kattan MW, Inoue Y, Giles FJ, et al. Cost-effectiveness of interferon-α and conventional chemotherapy in chronic myelogenous leukemia. *Ann Intern Med*. 1996;125:541-548.
33. Liberato NL, Quaglini S, Barosi G. Cost-effectiveness of interferon alfa in chronic myelogenous leukemia. *J Clin Oncol*. 1997;15:2673-2682.
34. Gulbrandsen N, Wisloff F, Nord E, et al. Cost-utility analysis of high-dose melphalan with autologous blood stem cell support vs. melphalan plus prednisone in patients younger than 60 years with multiple myeloma. *Eur J Haematol*. 2001;66:328-336.
35. Nord E, Wisloff F, Hjorth M, et al. Cost-utility analysis of melphalan plus prednisone with or without interferon-alpha 2b in newly diagnosed multiple myeloma. Results from a randomised controlled trial. *Pharmacoeconomics*. 1997;12:89-103.

36. Scott WG, Scott HM. Economic evaluation of third-line treatment with alemtuzumab for chronic lymphocytic leukaemia. *Clin Drug Investig*. 2007;27:755-764.
37. Wirt DP, Giles FJ, Oken MM, et al. Cost-effectiveness of interferon alfa-2b added to chemotherapy for high-tumor-burden follicular non-Hodgkin's lymphoma. *Leuk Lymphoma*. 2001;40:565-579.
38. Soini EJ, Martikainen JA, Nousiainen T. Treatment of follicular non-Hodgkin's lymphoma with or without rituximab: cost-effectiveness and value of information based on a 5-year follow-up. *Ann Oncol*. 2011;22:1189-1197.
39. Doss S, Hay N, Sutcliffe F. NICE guidance on bortezomib and thalidomide for first-line treatment of multiple myeloma. *Lancet Oncol*. 2011;12:837-838.
40. Kantarjian H, Mathisen M, Lipton J, O'Brien S. Having "skin in the game" and allowing cross-border importation of drugs can lower high cancer drug prices. *JAMA Oncol*. In press.
41. Bureau of Labor Statistics. Consumer Price Index—all urban consumers. http://data.bls.gov/cgi-bin/surveymost?cu. Accessed March 20, 2015.
42. Rennie D, Luft HS. Pharmacoeconomic analyses: making them transparent, making them credible. *JAMA*. 2000;283:2158-2160.
43. Rochau U, Sroczynski G, Wolf D, et al. Cost-effectiveness of the sequential application of tyrosine kinase inhibitors for the treatment of chronic myeloid leukemia. *Leuk Lymphoma*. 2015;14:1-22.
44. Ohm L, Lundqvist A, Dickman P, et al. Real-world cost-effectiveness in chronic myeloid leukemia: the price of success during four decades of development from non-targeted treatment to imatinib. *Leuk Lymphoma*. 2014;21:1-7.
45. Romero M, Chavez D, De Los Rios M, et al. Cost-effectiveness of nilotinib, dasatinib and imatinib as first-line treatment for chronic myeloid leukemia in Colombia. *Biomedica*. 2014;34:48-59.
46. Shanafelt TD, Borah BJ, Finnes HD, et al. The impact of ibrutinib and idelalisib on the pharmaceutical cost of treating chronic lymphocytic leukemia (CLL) at the societal level. *J Oncol Pract*. 2015;11:252-258.
47. American Society of Hematology. Analysis: high-cost blood cancer drugs deliver high value. http://www.hematology.org/Newsroom/Press-Releases/2014/3661.aspx Published February 5, 2015. Accessed March 23, 2015.
48. Goldberg P. Tufts researchers say blood cancer drugs are a good value; Kantarjian disagrees. http://www.cancerletter.com/articles/20150213_2. Published February 13, 2015. Accessed March 23, 2015.
49. Das K, Petigara T, Anderson G. Price negotiations for drugs in the U.S. http://hpm.org/en/Surveys/Johns_Hopkins_Bloomberg_School_of__Publ._H_-_USA/09/Price_Negotiations_for_Drugs_in_the_U.S..html Published April 2007. Accessed January 7, 2014.
50. Rome E. Big pharma pockets $711 billion in profits by price-gouging taxpayers and seniors. The Huffington Post. April 2007. http://www.huffingtonpost.com/ethan-rome/big-pharma-pockets-711-bi_b_3034525.html Accessed March 23, 2015.
51. Howard DH, Bach PB, Berndt ER, Conti RM. Pricing in the market for anticancer drugs. *J Econ Perspect*. 2015;29:139-162.
52. Zafar S, Peppercorn J, Schrag D, et al. The financial toxicity of cancer treatment: a pilot study assessing out-of-pocket expenses and the insured cancer patient's experience. *Oncologist*. 2013;18:381-390.
53. Dusetzina S, Winn A, Abel G, et al. Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. *J Clin Oncol*. 2014;32:306-311.
54. Chhatwal J, Kanwal F, Roberts MS, Dunn MA. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. *Ann Intern Med*. 2015;162:397-406.
55. AIDSMEDS. Treatments for HIV & AIDS. http://aidsmeds.com/list.shtml Accessed March 15, 2015.
56. Lopert R, Elshaug AG. Australia's 'fourth hurdle' drug review comparing costs and benefits holds lessons for the United States. *Health Aff (Millwood)*. 2013;32:778-787.