

Dynamic Cost-Effectiveness of Oncology Drugs

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Rapid increases in drug-related expenditures over the last several decades have led payers to focus increased attention on cost containment and the trade-off between the benefits of a drug and the drug's budget impact. An increasingly common method to estimate this trade-off is to perform cost-effectiveness analysis (CEA).¹ CEA provides a summary of value that is considered by payers to help inform their reimbursement policy for a drug.² The use of CEA by payers also influences drug expenditures and pricing,¹ which can subsequently have a significant impact on the pace and arrival of drug innovation.³⁻⁵ One important limitation of the current approach to conducting CEAs is that they are typically performed and attract the most attention at the time of initial drug launch or for individual indications; therefore, such analyses often disregard the overall cost-effectiveness of a single agent in the longer term, which can change dramatically over the life cycle of a drug.

The change in cost-effectiveness over time is especially important in the context of oncology drugs. The initial indication for a new oncology therapy is typically treatment of patients with late-stage disease for whom all approved treatment options have failed. It is challenging to demonstrate a large clinical benefit in patients with refractory disease who may have received multiple lines of therapy and may also have experienced toxicity from prior treatments. Subsequent indications tend to be for earlier lines of therapy, when patients are more robust and a greater clinical response is more likely. These populations also tend to be larger and, therefore, reflect a more common experience of patients treated with the drug. Therefore, CEA analyses focusing on the initial indication might not accurately capture the value of a drug over its life cycle for 2 important reasons. First, the patient populations receiving the drug can change substantially as new empirical evidence of the drug's effectiveness is published or new indications for the drug are approved. A second and important factor is that the costs of the drug for payers also change significantly over time due to loss of exclusivity and patent expirations, even though many oncology agents, such as paclitaxel, remain important elements of standard of care well after they have lost exclusivity.

The cost-effectiveness of a drug at initial launch, then, might be a poor approximation of the drug's cost-effectiveness over its

Abstract

Objective: To develop a methodology for computing cost-effectiveness measures of a drug throughout its life cycle.

Study Design: We developed a set of models that measure the long-term cost-effectiveness of 2 oncology drugs, paclitaxel and docetaxel, throughout their life cycles.

Methods: The study combined pricing history of the drugs, US Food and Drug Administration approval dates, drug utilization from Medicare claims, and clinical effectiveness information from phase III studies reported in the scientific literature. These data were used to estimate the incremental cost-effectiveness ratio (ICER) at the time of market entry and by year thereafter. The study population included patients with cancer who were treated with paclitaxel or docetaxel.

Results: The prices of paclitaxel and docetaxel dropped substantially due to patent expirations, while the number of users increased several fold because of subsequent empirical evidence and approval of new indications that resulted in greater efficacy. The ICER over a 10-year period was approximately 60% of the ICER at product launch for both drugs, and was further decreased when a longer-term perspective was taken.

Conclusions: We demonstrated that the ICER of a drug can decrease substantially over its life cycle. Thus, cost-effectiveness at drug launch might be a poor indicator of the long-term value of the drug. The results of this study are based on the analysis of 2 prominent oncology drugs, paclitaxel and docetaxel. The results may not be generalizable to other drug classes or other oncology drugs for which new indications are less common.

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life cycle. However, summary measures of a drug's cost-effectiveness that include the increasing efficacy in subsequent indications and as price declines are rarely presented. To our knowledge, only 1 other article, by Garrison and Veenstra,⁶ has included computations of the cost-effectiveness of a drug from a dynamic or life-cycle perspective. To do this, the authors simulated the change in cost-effectiveness of trastuzumab from the time of drug launch due to the introduction of a new indication.

In this article we add to the literature by estimating the cost-effectiveness of 2 oncology drugs, paclitaxel and docetaxel, over their life cycles. These 2 drugs were chosen because they have played an important role in improving cancer survival and because we are able to observe changes in prices and utilization of these drugs from product launch to the present. We extended prior research along several dimensions. First, we used data on drug utilization and prices to show how cost-effectiveness changes over a drug's life cycle from product launch to post-patent expiration. Second, we documented changes in cost-effectiveness due to new clinical evidence of efficacy, US Food and Drug Administration (FDA) approval of new indications, the size of the patient population treated, and changes in drug prices. Finally, we used Medicare claims data to construct a nationally representative sample to depict the ways in which the utilization of these drugs evolved over time by cancer type and year.

Methods

We developed the incremental cost-effectiveness ratios (ICERs) of 2 oncology drugs from a life-cycle perspective. These measures describe the net value of products over their life cycles rather than just at the time of product launch. The underlying model framework that we propose builds on the model developed by Garrison and Veenstra.⁶

To formally illustrate the difference between product life cycle and standard CEA measures, we first consider the ICER at product launch ($t = 0$), with the equation $ICER^0 = \frac{IC^0}{E^0}$, in which IC^0 is the incremental cost of the new drug at product launch and E^0 is the measure of incremental effectiveness of the drug at product launch.

Next, we consider the ICER T time periods after launch:

$$ICER^T = \frac{IC^0 p^0 + \beta IC^1 p^1 + \dots + \beta^T IC^T p^T}{E^0 p^0 + \beta E^1 p^1 + \dots + \beta^T E^T p^T}$$

In this equation, IC^T and E^T are the incremental cost and effectiveness of the drug T time periods after product launch, β is the time discount factor, and p^T is the population of users T periods after product launch. Given the definitions above, the ICER T time periods after product launch is simply the

ratio of the present value of incremental costs associated with the drug until period T (numerator) and the present value of the incremental effectiveness associated with the drug until period T . The ICER from a product life-cycle perspective is simply $ICER^T$, where T equals the end of the product life cycle.

Because drugs can last on the market for several decades, we calculate $ICER^T$ for 10 and 20 years after product launch.

Notice that $ICER^T = ICER^0$ only if the following 2 conditions are satisfied:

- 1) the incremental costs do not change over the life cycle $IC^T = IC^0$, and
- 2) the incremental efficacy does not change over the life cycle $E^T = E^0$.

If either of the above conditions are violated, then $ICER^T \neq ICER^0$. In this case, $ICER^0$ would be a poor approximation of the true long-term cost-effectiveness of drugs.

As discussed earlier, the first condition is likely violated because drug prices can decrease dramatically over the life cycle, with prices falling to as low as 10% of the product launch price after patent expiration. Notice that the effects of reduction in prices after product launch will be magnified by the increased diffusion of the drug over time; in other words, lower prices mean that a larger population will use the drug. This would increase the weight attached to costs in later years, when prices are low, and would correspondingly decrease the weight attached to costs in earlier years, when prices are high.

The second condition is also likely violated as the efficacy and effectiveness of the drug might change over its life cycle. As mentioned above, this is especially likely for oncology products, which are initially used as second- or third-line treatment for patients with late-stage cancers; after product launch many oncology drugs receive approval for additional indications, such as treatment of early-stage disease and/or other types of cancers. As was the case with changes in price, the effects of changes in effectiveness will be magnified by the increased diffusion of the drug over time; in other words, increased effectiveness translates into greater diffusion of the drug. This would increase the weight attached to effectiveness in periods when efficacy is increased. To compute the ICER from a life cycle perspective we need information on the measures described below.

Measures

Incremental costs by indication. We estimated incremental costs by indication by using cost-effectiveness data published in peer-reviewed journal articles whenever possible. For some indications approved in the early 1990s, when cost-effectiveness data were often not available, we estimated

■ **Table 1.** Date of FDA Approvals and ICER by Indication and Year

Drug	Indication	FDA Approval Date	First Published Effectiveness	Incremental Cost (\$) ^a	Life-Years Gained	Source of ICER
Paclitaxel	Ovarian cancer (second line)	12/29/1992	n/a	No data	n/a	n/a
	Breast cancer (second line)	4/13/1994	Holmes et al (1991) ¹⁰	12,001	0.23	Nabholtz et al (1996) ¹¹ ; Henderson et al (1989) ¹²
	Kaposi's sarcoma (second line)	8/4/1997	n/a	No data	n/a	n/a
	Ovarian cancer (first line)	4/9/1998	McGuire et al (1996) ¹³	13,756	0.65	Covens et al (1996) ¹⁴
	Lung cancer (first line)	6/30/1998	Hainsworth et al (1997) ¹⁵	10,678	0.13	Earle and Evans (1999) ¹⁶
	Breast cancer (adjuvant)	10/25/1999	Demetri et al (1997) ¹⁷	6,478	0.3 ^b	Limwattananon et al (2006) ¹⁸
	Docetaxel	Breast cancer (second line)	1/6/1998	van Oosterom (1995) ¹⁹	7,562	0.22
Lung cancer (second line)		12/23/1999	Fossella et al (1995) ²¹	14,954	0.34	Leighl et al (2002) ²²
Lung cancer (first line)		11/27/2002	n/a	n/a	Not significant	n/a
Prostate cancer		5/19/2004	Picus and Schultz (1999) ²³	13,936	0.2	Collins et al (2007) ²⁴
Breast cancer (adjuvant)		8/18/2004	Smith et al (2002) ²⁵	12,113	0.37	Wolowacz et al (2008) ²⁶
Gastric cancer		3/22/2006	n/a	No data	n/a	n/a
Head and neck cancer		10/17/2006	Posner et al (2001) ²⁷	3,728	2.1 ^b	Parthan et al (2009) ²⁸

FDA indicates US Food and Drug Administration; ICER, incremental cost-effectiveness ratio.

^aAll costs are in 2010 US dollars.

^bQuality-adjusted life-years.

the incremental cost of treatment using information on unit prices and treatment regimens from published data and/or FDA product labels, including dosage and average number of courses.

Drug prices over the life cycle. To estimate the incremental costs for a given indication change over the life cycle of the drug due to changes in real drug prices, we obtained the wholesale acquisition cost (WAC) of paclitaxel and docetaxel in branded and generic forms (if applicable) from Analy\$ourceOnline. These data were obtained from a national drug database, and are included with permission from and copyrighted by First DataBank, Inc. Information on the methodology of collecting price data is described at the First DataBank website: <http://www.firstdatabank.com/Support/drug-pricing-policy.aspx>. When multiple prices were posted for a single year, the lowest WAC available for that year was used. All costs and prices shown in this article are inflation-adjusted to 2010 US dollars, assuming an annual inflation rate of 3%.

Utilization rates by indication. For each drug we constructed nationally representative utilization rates by can-

cer type or indication from 1991 to 2007. The utilization data were derived from the surveillance, epidemiology, and end results (SEER) Medicare data and include the number of Medicare patients using each drug by major cancer categories, including breast, lung, prostate, and colorectal cancer. Because no utilization data are available for the time period after 2007, we assumed that utilization rates stayed at the 2007 levels for future years. The data were weighted to be nationally representative using information on national estimates of prevalence of different types of cancer by year. In particular, we assumed that the utilization rate of different drugs by cancer type is the same for Medicare and non-Medicare beneficiaries; therefore, national estimates of prevalence of different cancers multiplied by the utilization rates of different drugs by cancer type from SEER Medicare provide an estimate of the national utilization of drugs by cancer type.

Effectiveness. We also quantified life-cycle changes in efficacy. For each drug we identified the approval of new indications over the product life cycle from the FDA product labels, and the life-years gained for each new indication from

peer-reviewed journal articles. We omitted certain indications (such as paclitaxel for second-line treatment of ovarian cancer and Kaposi's sarcoma, and docetaxel for first-line treatment of non-small-cell lung cancer and gastric cancer), as no reliable data on cost-effectiveness were available or could be constructed for these indications. We combined these data with claims-based measures of the indication-specific utilization described above, in order to produce time-varying estimates of mean life-years gained. These estimates change with the introduction of new indications, as well as with shifts in the proportion of patients treated for newer or older indications over time.

Imputations in the Absence of Price and Utilization Data

In order to illustrate the long-run perspective, we calculated the ICERs of each drug for 20+ years since product launch. For paclitaxel we covered the years 1994 to 2016. For the 5 years beyond 2011, for which actual price data were not available, we assumed the real price of paclitaxel stayed constant at the 2011 level until 2016. For docetaxel, we covered the time period of 1998 to 2020. Because the docetaxel patent expired recently (in 2010), and we have not had a chance to observe price drops over a long period of time after the loss of exclusivity, as in the case of paclitaxel, we assumed its price would decrease at the same rate as that of paclitaxel after its loss of exclusivity, and imputed the annual prices of docetaxel between 2012 and 2020 using a linear prediction model. The data on utilization rates by indication were not

available beyond the year 2007, and we assumed that the rates stayed at the same level of year 2007 for future years in our model.

Sensitivity Analysis

The credibility of the results depends upon their robustness to alternate assumptions about the life cycle trajectory of each of the key model inputs described above. We therefore tested the robustness of our results with multiple 1-way sensitivity analyses, by varying the values of the incremental cost and life-years gained to plus or minus 25%.

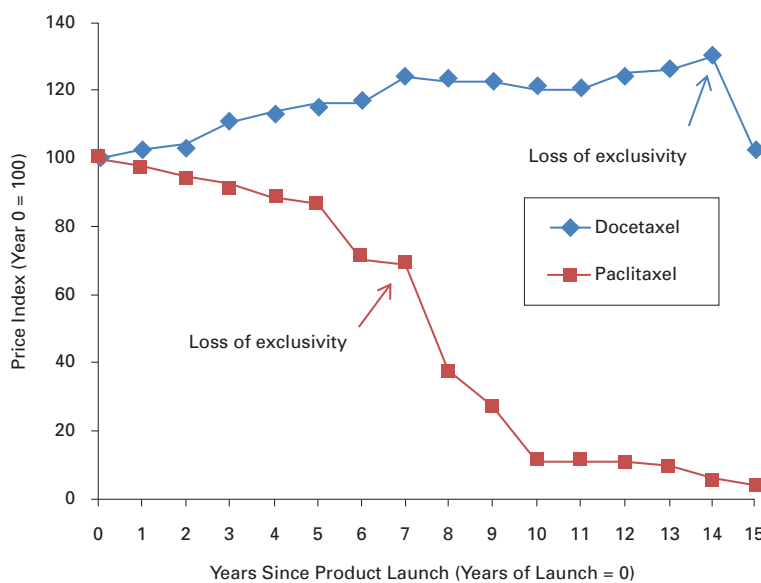
Results

New Indications and New Data on Cost-Effectiveness

Several new indications were approved for both paclitaxel and docetaxel within 10 years of product launch (Table 1). In general, the effectiveness of the 2 drugs for new indications was greater than the effectiveness of their original indications at product launch. Two exceptions were a new indication for paclitaxel for the treatment of lung cancer and a new indication for docetaxel for the treatment of metastatic prostate cancer; however, both conditions are associated with a poor prognosis. Table 1 also shows that the empirical evidence on effectiveness in peer-reviewed journal articles usually predates its official FDA indication approvals by a few years.

Fifteen Years of Pricing History Since Product Launch

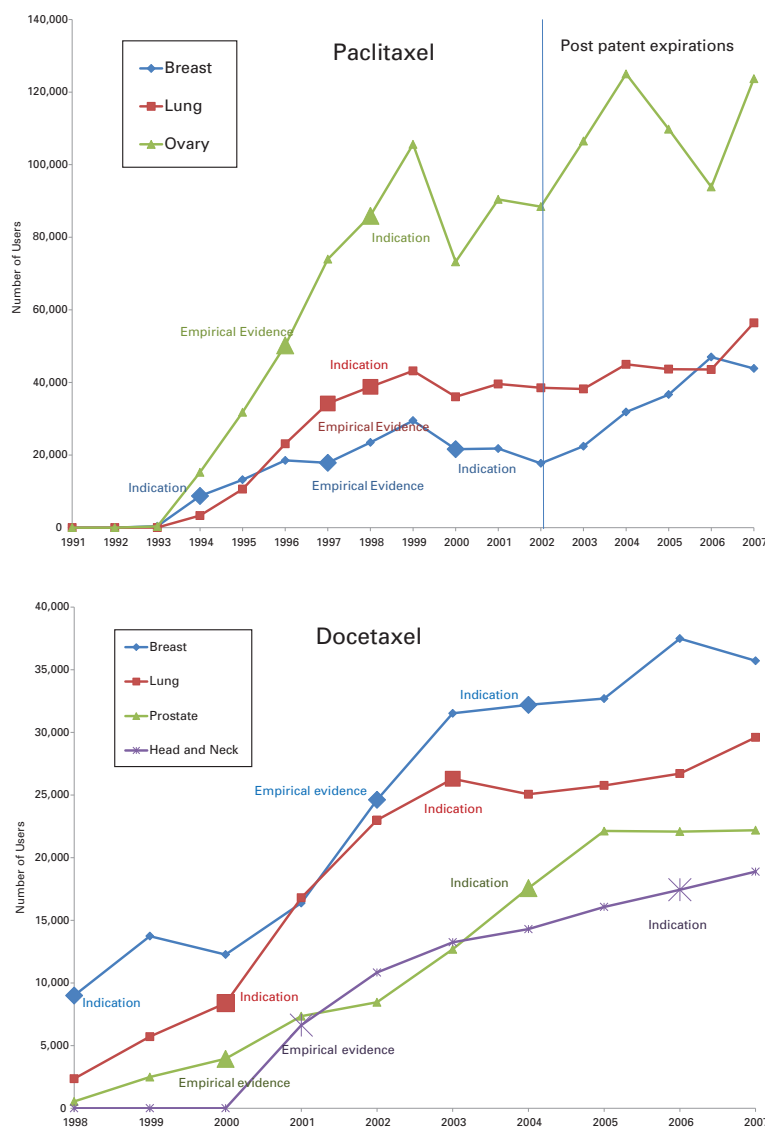
■ Figure 1. Changes in Real Prices of Paclitaxel and Docetaxel Over Their Life Cycles^a



^aPrior to being indexed, all drug prices were inflation-adjusted to 2010 US dollars.

Figure 1 shows the trends in real prices for paclitaxel and docetaxel in 2010 US dollars. The prices are rescaled so that the initial price in the year of product launch equals 100; this allows for easy comparisons of product prices over the life cycle relative to price at product launch. Figure 1 demonstrates that the price of paclitaxel decreased after product launch, with real prices being approximately 30% lower 6 years after product launch. There was also a sharp decline in prices after loss of exclusivity due to patent expirations; the price of paclitaxel 12 years after product launch was only 10% of its price at product launch. In contrast, the price of docetaxel increased gradually after product launch, rising to approximately 17% higher 6 years after product launch and 24% higher 12 years after product launch. Subsequently, the price of docetaxel declined by approxi-

Figure 2. Number of Paclitaxel and Docetaxel Users by Cancer Type Over Time



Empirical evidence indicates the year in which findings on the clinical effectiveness of the drug for a new indication were first published in a peer-reviewed journal. Indication indicates the year in which a new indication was approved by the US Food and Drug Administration. During the years in which new evidence was available, the data points are enlarged and labeled on the graph.

mately 25% in a single year after it lost exclusivity in 2011 due to patent expirations.

Utilization Rates and New Evidence of Efficacy

Figure 2 shows the time trends in the utilization of paclitaxel and docetaxel by cancer type, demonstrating that the utilization of both drugs changed in response to publication of clinical evidence of new indications and regulatory approval of new indications. Figure 2 also shows that for

both paclitaxel and docetaxel, increased use for an indication began quickly after clinical data showed effectiveness, usually some time before the official approval of the new indication. In 2007 there were 8 times as many paclitaxel users as in 1994, when the first cost-effectiveness data on paclitaxel became available. Also in 2007 there were 9 times as many docetaxel users as in 1998, when docetaxel was first launched. Thus, the most common use of the products is generally for the approved indications for which efficacy is greatest. This use is much more widespread after loss of exclusivity than at the time of product launch.

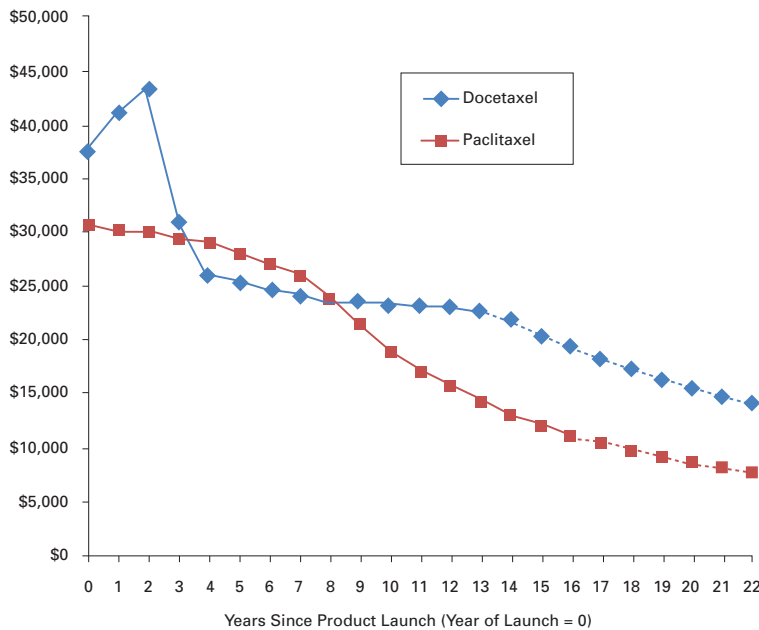
Dynamic Cost-Effectiveness

The ICERs of paclitaxel and docetaxel over 22 years are shown in Figure 3. The ICERs of both drugs decrease as one takes a longer-term perspective; for example, the ICER at year 0 or at product launch was \$30,723 per life-year gained for paclitaxel and \$37,537 per life-year gained for docetaxel. The ICER over a 10-year time period is only a fraction of the ICER at product launch. In particular, the ICER of paclitaxel over a 10-year time period was 61% of its ICER at product launch and, similarly, the ICER of docetaxel over a 10-year time period was 60% of its ICER at product launch. The ICERs of both drugs decreased even further when viewed with a 15- and 20-year perspective; specifically, the ICER of paclitaxel over a 20-year period was \$8,563 per life-year gained (28% of the ICER at launch) and the ICER of docetaxel over a 20-year period was \$15,468 per life-year gained (41% of the launch ICER). The 1-way sensitivity analyses produced a range of ICER values but do not change the main qualitative results of the study (Table 2).

Discussion

The ongoing debate over rising healthcare spending has led to additional scrutiny of the value of healthcare interventions, including pharmaceuticals. This movement has also resulted in keen interest in CEAs, which have been adopted as a standard for reimbursement approval in countries such as the United Kingdom. Although CEA is often conducted at product launch or for specific indications in isolation, and is an important component of dossiers submitted to public and

Figure 3. Dynamic Incremental Cost-Effectiveness Ratio of Paclitaxel and Docetaxel Since Product Launch



Data for the time period beyond year 2011 are imputed and shown with a dotted line.

private payers,⁷ the initial CEA or CEAs for new indications might not reflect the true long-term value of a particular drug. For this reason, the initial CEA needs to be placed into context against a summary measure of CEAs that reflects long-term value.

There are several important reasons that standard CEA methods might not accurately capture long-term drug value, one of which is the impact of new indications and/or patient populations. This is particularly important for oncology products, since ethical considerations and the difficulty in obtaining regulatory approval typically dictate that an investigative compound be initially tested for second- or third-line therapy for patients with advanced disease, who are relatively small in number and have limited proven treatment options. If the new drug is effective in the initial clinical setting, new clinical trials will typically be initiated to determine safety and efficacy of the product as first-line treatment or adjuvant treatment

(chemotherapy following curative surgery) for the same cancer or for other types of cancers. Our findings, which are supported by Garrison and Veenstra,⁶ show that these subsequent uses in less severely ill patients tend to be associated with better clinical benefit and more favorable cost-effectiveness. In addition, we have shown that patients treated for subsequently approved indications are more numerous, so that the experience of greater benefit and better cost-effectiveness is more characteristic of patients' experience with the drug.

Another facet of standard CEA conducted at product launch is that it evaluates costs when they are at their maximum. Drug prices might decrease over their life cycles, especially after the entry of generics after patent expirations; therefore, prices at launch might be a poor indicator of costs of the drug over its life cycle.

Given that standard CEA might not capture the long-term value of drugs, innovative approaches to measuring the cost-effectiveness of new drugs over the entire product life cycle are needed in order to capture the overall value of new drugs over time. Comparing long-term value with value at product launch can inform the debate on appropriate use of CEA for reimbursement and coverage decisions.

Table 2. Sensitivity Analysis

Results	Cost (-)	Cost (+)	LYG (-)	LYG (+)
Paclitaxel				
Life-cycle ICER at Year 0	23,043	38,404	40,965	24,579
Change from baseline value (%)	-25	+25	+33	-20
Life-cycle ICER at Year 10	14,165	23,609	25,183	15,110
Change from baseline value (%)	-25	+25	+33	-20
Life-cycle ICER at Year 20	6,422	10,704	11,418	6,851
Change from baseline value (%)	-25	+25	+33	-20
Docetaxel				
Life-cycle ICER at Year 0	28,153	46,921	50,049	30,030
Change from baseline value (%)	-25	+25	+33	-20
Life-cycle ICER at Year 10	17,434	29,056	30,994	18,596
Change from baseline value (%)	-25	+25	+33	-20
Life-cycle ICER at Year 20	11,601	29,056	20,624	12,374
Change from baseline value (%)	-25	+25	+33	-20

ICER indicates incremental cost-effectiveness ratio; LYG, life-years gained.

In this article we presented our findings after developing and estimating the life cycle CEA for 2 important oncology agents. We demonstrated that the ICER of a drug can decrease substantially over its life cycle, thus creating value net of costs. The ICER of paclitaxel decreased by 39% at 10 years after product launch and by 72% at 20 years after product launch. Similarly, the ICER of docetaxel decreased by 38% at 10 years after product launch and by 59% at 20 years after product launch. The ICER from a life cycle perspective responded to the discovery of new indications when they were typically more cost-effective than indications at first product launch and were more typical of patients' experience. The sharp decline in prices after patent expirations is also an important determinant of ICER, with its importance increasing over a longer-term horizon of 20 years.

It should be noted that the ICER calculated by a public plan may be different from that calculated by a private plan. For example, Medicaid prices are often lower than private payer prices due to mandated rebates. In addition, because there are various manufacturer rebates and copay assistance programs for patients with cancer, the ICER of a drug can even be different at the individual person level; however, such price differences should not change the general trend of a drug's ICER continuing to decrease over time.

The findings of this study should be viewed in light of its limitations. First, the data on drug utilization are limited to Medicare beneficiaries and are thus not based on a nationally representative sample of individuals. To overcome this limitation, we weighted the data using supplemental information on national rates of cancer prevalence. Second, WAC does not represent the true acquisition costs of drugs, as it excludes rebates and discounts received by health plans. We are therefore likely overestimating drug costs and ICERs, especially before loss of exclusivity, when sizable rates are common. Third, our estimates do not capture improvements in the efficacy and cost-effectiveness of a drug over time as physicians learn how to better manage therapy. For example, in the case of high-risk leukemia and difficult-to-treat neuroblastoma, event-free survival improved when the standard agents (methotrexate and melphalan, respectively) were administered differently or combined with different drugs.^{8,9} We were not able to measure such improvement in this article due to the difficulty of obtaining real-world data on adoption of best practices over time and relating the data to clinical outcomes. Finally, it is important to note that the results of this study might not be generalizable to other therapeutic classes or other oncology drugs. For example, highly complex biologics can remain competitive even after patent expirations because they are difficult to replicate, possibly

resulting in less pricing reduction at the end of exclusivity. Nevertheless, Garrison and Veenstra⁶ showed that the ICER of trastuzumab, also a biologic, declined to less than half the original level even before loss of exclusivity because its second indication, to treat early-stage breast cancer, shows greater efficacy as well as more favorable cost-effectiveness and is applicable to a larger number of patients.

Conclusions

While evidence shows that various factors can cause the ICER of a drug to decrease in the long term, there remains great uncertainty at the time of a specific drug's product launch about how its ICER will evolve over time. One direction for future research might be to create a predictive tool that estimates the predicted long-term dynamic ICER for a specific drug at product launch. Several sources of information might be useful in creating such a predictive tool. First, historical information on the use of other drugs in the same drug class or with the same mechanism of action might help shed light on how the use of a particular drug might evolve over time. Second, evidence from completed and ongoing clinical trials might suggest future new indications for the drug and might also be useful in predicting the risk of black-box or safety warnings. Third, evidence from early postmarket studies might also help to predict how the use of a drug might evolve over its life cycle. All these sources of information can be used together to predict the probability of different events over a drug's life cycle. Both positive events, such as new indications that expand the use of a drug, and negative events, such as black-box warnings and product withdrawals that restrict the use of the drug, should be considered. These data on the probability of different events should be combined with data on drug prices and potential patient populations to predict the long-term ICER of a drug. Finally, due to great uncertainty at product launch, sensitivity analyses should be performed to consider ICER under a range of future scenarios. Such data will eventually help decision makers make more informed decisions about drug coverage and reimbursement.

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Report

Authorship information: Concept and design (YL, JRP, TP, NS, SW); acquisition of data (TP, JRP, SW); analysis and interpretation of data (YL, JRP, TP, NS, SW); drafting of the manuscript (YL, JRP, TP, NS, SW); critical revision of the manuscript for important intellectual content (YL, JRP, TP, NS); statistical analysis (YL, NS); obtaining funding (JRP); and supervision (NS).

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