

The Option Value of Innovative Treatments in the Context of Chronic Myeloid Leukemia

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Traditional health-technology assessment, such as cost-effectiveness analysis, measures the value of a health innovation by comparing benefits (eg, survival gains or improved quality of life) to costs, assuming no further improvements in medical technology aside from the innovation in question.¹ Such methods overlook the fact that life-extending innovations can allow patients to live until the next breakthrough, which may offer additional survival opportunities. This possibility of benefiting from future improvements in medical technology is the “option value” of a health innovation. As long as medical technology continues to advance, there will be option value in survival-improving innovations. Failing to account for this value ignores a potentially important source of benefit to patients, understating the effectiveness of new therapies, especially in areas of rapid innovation.

The existence of option value has been demonstrated in the context of end-of-life care from the perspective of economic theory² but, with a few exceptions,³ option value has not been incorporated into existing assessments of pharmaceutical innovation. Because the literature lacks both a guide to incorporating option value into health-technology assessment and a method for calculating the option value of current technologies, real-world demonstrations are needed to illustrate the feasibility and necessity of incorporating option value into practice. In the context of healthcare management, option value assessments are key to achieving a better understanding of the overall effectiveness of innovative treatments that may ultimately lead to significant improvements in patient care.

The latest breakthroughs in chronic myelogenous leukemia (CML) treatment serve as a prominent example of the relevance of the option-value concept. (See the [eAppendix](#) at www.ajmc.com for a list of agents used for CML treatment since 1959 and the dates of their approval by the US Food and Drug Administration.) Historically, survival has been 3 to 5 years from the time of CML diagnosis.⁴ However, the introduction of tyrosine kinase inhibitors (TKIs), an innovative class of targeted therapies, has led to substantial survival gains in the treatment of CML, with overall survival of patients in clinical trials increasing to 89% at 5 years.⁵ Treatment with the first-generation TKI imatinib rapidly became the standard of care after the drug was introduced

Abstract

Objective: To quantify in the context of chronic myeloid leukemia (CML) the additional value patients receive when innovative treatments enable them to survive until the advent of even more effective future treatments (ie, the “option value”).

Study Design: Observational study using data from the Surveillance, Epidemiology and End Results (SEER) cancer registry comprising all US patients with CML diagnosed between 2000 and 2008 (N = 9,760).

Methods: We quantified the option value of recent breakthroughs in CML treatment by first conducting retrospective survival analyses on SEER data to assess the effectiveness of TKI treatments, and then forecasting survival from CML and other causes to measure expected future medical progress. We then developed an analytical framework to calculate option value of innovative CML therapies, and used an economic model to value these gains. We calculated the option value created both by future innovations in CML treatment and by medical progress in reducing background mortality.

Results. For a recently diagnosed CML patient, the option value of innovative therapies from future medical innovation amounts to 0.76 life-years. This option value is worth \$63,000, equivalent to 9% of the average survival gains from existing treatments. Future innovations in CML treatment jointly account for 96% of this benefit.

Conclusions: The option value of innovative treatments has significance in the context of CML and, more broadly, in disease areas with rapid innovation. Incorporating option value into traditional valuations of medical innovations is both a feasible and a necessary practice in health technology assessment.

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as first-line treatment in 2001.^{6,7} Imatinib remained the only TKI approved for CML treatment for several years until the introduction of 2 second-generation agents. Dasatinib was approved for second-line use in June 2006, representing a breakthrough for CML patients failing imatinib; long-term follow-up of these patients showed that the vast majority (78%) were alive at 5 years.⁸⁻¹⁴ In 2007, nilotinib was also approved for second-line use.^{15,16} While dasatinib and nilotinib were initially approved for second-line use, these agents demonstrated superiority to imatinib in the first-line setting and were approved for this indication in 2010.^{8,17}

In this study we quantified the extent to which the first-generation TKI served as a “bridge” to subsequent CML treatments, and how treatment with first- and second-generation TKIs is allowing patients to survive into periods of future improvements in CML treatment and background mortality. For this purpose we developed an analytical framework to enable incorporation of option value into health-technology assessment. We used a Cox proportional hazards model to estimate historical real-world CML survival trends, and employed the Lee-Carter method to forecast future survival from any cause of death in the Surveillance, Epidemiology and End Results (SEER) cancer registry. Based on these estimates we quantified the option value of innovative TKI therapies and used an economic model^{2,18} to express these gains in dollar terms.

Methods

Conceptual Framework

As discussed previously, option value is the additional survival benefit patients receive when innovative treatments enable them to experience future medical breakthroughs; stated more simply, it is the benefit derived from the opportunity to live longer. Measuring the option value of a treatment is feasible to the extent that there are available data on treatment effectiveness and future (post-treatment) survival. As an illustration of this point, assume that half of the patients suffering from a terminal disease experience a 1-year life extension due to innovative Therapy A, while the remaining half do not survive; hence, the life expectancy gain from Therapy A is 0.5 life-years. Next, suppose that, after 1 year, surviving patients gain access to a new medical innovation (Therapy B) that allows them to live an additional 4 months (ie, 0.33 life-years = 4/12); thus, the estimated option value of Therapy A is 2 months (or 0.16 life-years, computed as the product of 0.5 life-years from Therapy A effectiveness and 0.33 life-years from future access to Therapy B). A more detailed explanation of this concept is presented in the eAppendix, along with the analytical framework to assess the

value of a health innovation and incorporate its option value.

In the context of CML, initial assessments of benefits comparing TKI therapy with the previous standard of care underestimate the value of TKI therapy by ignoring its option value. In particular, the option value of first-line treatment includes: 1) reductions in background mortality through future medical innovations, and 2) survival improvements that enable patients who develop treatment resistance to survive with greater probability into a period during which second-generation agents become available. These benefits have not been previously estimated.

Data

SEER is the gold standard registry for cancer in the United States. SEER registries identify incident cases of malignancies based on uniform reporting, according to the *International Classification of Disease for Oncology, 3rd Edition (ICD-03)*. As the only national cancer database that follows patients over time to trace survival, SEER contains information on 21,558 individuals diagnosed with CML between 1973 and 2008. The data set includes type(s) of cancer (up to 10 tumors), age at diagnosis, year of diagnosis, gender, race, ethnicity, marital status, county of residence, and time and cause of death.

Patients with CML were identified in the SEER registry based on ICD-03 codes 9863 (chronic myeloid/myelogenous leukemia), 9875 (chronic myelogenous leukemia, BCR/ABL-positive), and 9876 (atypical chronic myeloid leukemia, BCR/ABL-negative). Because imatinib was introduced in 2001, we restricted the sample to CML patients diagnosed in 2000 or later. Patients diagnosed in 2000 served as the control (pre-treatment) group in order to measure the cost of delaying treatment by 1 year. **Table 1** presents summary statistics for the restricted sample; specifically, for patients diagnosed between 2001 and 2005 (the time period when first-generation TKI treatment became available) and for patients diagnosed after 2006 (the time period when second-generation treatments became available). As a sensitivity analysis, we considered control groups diagnosed with CML up to 5 years prior to 2000. The results are quantitatively similar and shown in the eAppendix. The 2000 to 2008 sample consists primarily of white (82%) and male (58%) patients. More than half (52%) of the patients are married, and the average age at diagnosis was 62 years. Approximately 5 of every 6 patients have only 1 primary cancer (CML), and the average mortality from CML and other causes in the period of analysis is 26% and 11%, respectively. Aside from mortality, patient characteristics are similar across control and treatment groups. Mortality from CML was 25% lower among

■ **Table 1.** SEER Summary Statistics

	Total Sample	Control Group	First-Generation TKI	Second-Generation TKI
Year(s)	2000-2008	2000	2001-2005	2006-2008
Death from CML	0.26	0.40	0.30	0.14
Standard deviation	(0.44)	(0.49)	(0.46)	(0.35)
Death from other cause	0.11	0.14	0.13	0.06
Standard deviation	(0.31)	(0.35)	(0.34)	(0.25)
Fraction male	0.58	0.57	0.58	0.58
Standard deviation	(0.49)	(0.49)	(0.49)	(0.49)
Age at diagnosis	61.95	61.54	62.37	61.44
Standard deviation	(19.61)	(19.56)	(19.52)	(19.75)
Number of tumors	1.22	1.21	1.23	1.22
Standard deviation	(0.49)	(0.47)	(0.49)	(0.49)
Fraction white	0.82	0.84	0.83	0.82
Standard deviation	(0.38)	(0.37)	(0.38)	(0.39)
Fraction black	0.09	0.08	0.09	0.09
Standard deviation	(0.28)	(0.28)	(0.29)	(0.28)
Fraction Asian	0.06	0.07	0.06	0.06
Standard deviation	(0.24)	(0.26)	(0.24)	(0.24)
Fraction other race	0.03	0.01	0.02	0.03
Standard deviation	(0.16)	(0.10)	(0.15)	(0.18)
Fraction Hispanic	0.11	0.10	0.10	0.12
Standard deviation	(0.31)	(0.30)	(0.30)	(0.32)
Married at diagnosis	0.52	0.53	0.52	0.51
Standard deviation	(0.50)	(0.50)	(0.50)	(0.50)
Observations	10,423	1,204	5,646	3,573

CML indicates chronic myeloid leukemia; SEER, Surveillance, Epidemiology and End Results; TKI, tyrosine kinase inhibitor.

patients diagnosed with CML between 2001 and 2005, relative to patients diagnosed before the introduction of first-generation treatment. Other-cause mortality, or mortality due to causes different from CML, is similar across the first-generation treatment and control groups. Additionally, both CML and other-cause mortality are substantially smaller among patients diagnosed between 2006 and 2008 relative to patients diagnosed before 2005. This is driven largely by a shorter follow-up period for the second-generation treatment group, resulting in greater censoring of CML and other-cause mortality.

Statistical Analysis

We combined 2 distinct statistical analyses to compute the option value of TKIs. First, we employed a Cox proportional hazards model¹⁹ to calculate past improvements in CML survival and survival from diseases different from CML between 2000 and 2008. Second, we used the Lee-Carter

method to forecast future improvements in CML and other-cause mortality several decades into the future.

We estimated the direct survival gains from TKIs by first applying the Cox model to the SEER sample of patients diagnosed with CML between 2000 and 2008. We included year of diagnosis as the key explanatory variable to generate year-specific survival curves. To mitigate potential bias from unobservable factors, we controlled for a rich set of patient characteristics that affect mortality independently of year of diagnosis, including age at the time of CML diagnosis, month of CML diagnosis, number of other cancers at diagnosis, and other demographic variables. The eAppendix describes the Cox proportional hazards model and shows the regression estimates. Next, we developed an algebraic method to identify survival associated with first- or second-line TKI treatment from the year-specific survival curves observed between 2000 and 2008. This algebraic method is explained in the eAppendix. Year-specific survival curves

■ **Table 2.** The Option Value of Innovative CML Therapies

	First-Line TKI	Second-Line TKI	Average ^a
(Column)	(1)	(2)	(3)
Life expectancy ^b	16.14	14.60	15.68
Gains from innovation against CML mortality			
Survival gain (life-years)	7.55	6.01	7.09
Option value			
Life-years	0.75	0.69	0.73
Fraction of survival gain	9.9%	11.5%	10.3%
Dollars ^c	\$64,343	\$56,539	\$62,092
Gains from innovation against non-CML (background) mortality			
Survival gain (life-years)	1.99	0.82	1.64
Option value			
Life-years	0.04	0.02	0.03
Fraction of survival gain	1.8%	2.3%	1.9%
Dollars ^c	\$1,653	\$434	\$1,238
Total gains from innovation against all-cause mortality			
Survival gain (life-years)	9.54	6.82	8.73
Option value			
Life-years	0.78	0.71	0.76
Fraction of survival gain	8.2%	10.4%	8.7%
Dollars ^c	\$65,996	\$56,973	\$63,330

CML indicates chronic myeloid leukemia; TKI, tyrosine kinase inhibitor.

^aWeighted average based on a probability of failing first-line treatment of 0.30.

^bThe life expectancy of a CML patient in the control group diagnosed in 2000 is 8.59 years.

^cGains valued according to Becker et al¹⁸ and Philipson et al.²

were weighted by population survival probabilities in the United States from the Human Mortality Database (HMD) to obtain nationally representative survival data of the CML population. HMD life tables are based on population estimates from the US Census Bureau, and birth and death reporting from the Census Bureau and the National Center for Health Statistics. We accounted for treatment resistance by incorporating estimates of the probability of resistance to first-line treatment from the existing literature.²⁰ Given the sample's limited time span, survival past 7 years from diagnosis was assumed to decline at the rate of the general population based on the HMD. A sensitivity test to evaluate the implications of this assumption is presented in the Discussion section.

The second part of the statistical analysis forecasted improvements in CML and other-cause survival from 2000 to 2055 by applying the Lee-Carter method to the year-specific (2000-2008) SEER survival curves. This method involved modeling age-specific mortality rates in terms of a long-term trend in overall mortality and an age-specific response to the

overall trend.^{21,22} Furthermore, sensitivity analyses tested the robustness of our results to alternative survival forecasts. The eAppendix describes the Lee-Carter method in detail and presents sensitivity analyses where the option value of innovative CML treatments is recalculated using the lower and upper bounds of the survival forecasts' 95% confidence intervals.

We calculated the option value of innovative TKI treatments relative to the survival profile of a CML patient with the average age in the sample (62 years) diagnosed in 2000. Finally, we used an economic model based on previous work by Becker et al¹⁸ and Philipson et al² to express option value in monetary terms. This economic model is described in the eAppendix.

Results

The option value of innovative TKI therapies, accounting for medical progress in CML and background mortality, is shown in **Table 2**. These gains were quantified in the context of 3 possible scenarios. The first scenario (column 1) represents the survival gain and option value derived from first-

line therapy for patients who have not developed resistance to treatment, relative to patients in the control group. This option value arises from future reductions in all-cause mortality, future advances in first-line treatment of CML, and future availability of second-line therapies if first-line treatment fails. The second scenario (column 2) represents the survival gain and option value of second-line therapy for patients in whom first-line treatment fails, as compared with patients in the control group. This option value is generated by future reductions in all-cause mortality, advances in second-line treatment of CML, and future availability of third-line therapy if second-line treatment fails. Calculating the weighted average of columns 1 and 2 reveals the third scenario (column 3) as the expected survival gain and option value for a recently diagnosed hypothetical CML patient with access to second-line therapies if first-line treatment fails.

Per the results in Table 2, there is almost negligible option value among CML patients from medical progress against background mortality (ie, 0.02-0.04 life-years) even though TKIs provide non-negligible survival benefits against other diseases (ie, 0.82-1.99 life-years). The option value of first-line treatment with imatinib as a bridge to further innovation in CML treatment alone (and not other diseases) accounts for 96% of the total option value.

First-line treatment provides an estimated total life expectancy gain of 9.54 life-years in CML patients who do not experience treatment failure, as compared with the control group (Table 2, column 1). In addition, future medical progress in CML treatment and background mortality provides patients who have not developed resistance to first-line treatment an option value of 0.78 life-years, or 8.2% of the total life-expectancy gain. Conversely, second-line treatments provide an estimated total life-expectancy gain of 6.82 life-years in CML patients who have experienced first-line treatment failure (Table 2, column 2). For these patients, the option value of second-line treatment from future medical progress against CML and background mortality is 0.71 life-years, or 10.4% of the total life-expectancy gain. On average, the option value of innovative TKI treatments for a recently diagnosed CML patient is 0.76 life-years, or 8.7% of the 8.73 expected life-year gain from first- and second-line treatments (Table 2, column 3).

Expressing all life-year gains as a private monetary valuation,^{2,18} the option value of first-line treatment is worth approximately \$66,000. For patients who develop resistance to first-line treatment, the option value of second-line treatment is worth nearly \$57,000. Newly diagnosed patients have an average (or expected) option value of 0.76 life-years, worth approximately \$63,000.

Discussion

For this study we developed an analytical framework for incorporating option value into the standard calculation of the value of a health innovation, and applied this framework to the case of innovative CML therapies. While economic theory suggests the presence of option value in the context of medical treatment, this source of value has been ignored in the literature on health technology assessment. This study is among the first applications of option value to the assessment of pharmaceutical innovation, and the first to measure option value prospectively.

Our findings show that, in the context of CML, the option value of innovative TKI therapies is equivalent to 9% of their average survival gain. Thus, ignoring the option value of these treatments underestimates their effectiveness by approximately 9%. In monetary terms, an option value of \$63,000 is a sizable benefit, especially when compared with the annual costs of TKI therapies, which range from \$30,000 to \$70,000.²³ Although a thorough cost-effectiveness analysis of these therapies would require an assessment of the costs incurred in the additional years of life extension, our findings suggest that the option value may fall within the range of costs for the first year of TKI treatment.

An intrinsic limitation of our study is that option value estimates depend on forecasts of future improvements in CML and other-cause survival. Although forecasts are inherently uncertain and not definitive, ours were based on high-quality and representative data on historical survival gains. A sensitivity analysis addressed this issue by recalculating option value at the lower and upper bounds of the survival forecasts' 95% confidence intervals; this sensitivity analysis is shown in the eAppendix. Proceeding from the least to the most optimistic forecast scenario, the average option value of a newly diagnosed patient increased from 0.36 life-years (with a net worth of \$34,000) to 1.16 life-years (with a net worth of \$92,000).

Given the limited time-span of our sample (2000-2008), we assumed survival past 7 years from diagnosis declined at the same rate as in the general population, based on the HMD. Although this assumption forces survival curves in the treatment and control groups to decay at the same rate, it is conservative to the extent that the control group's survival curve may actually decay at a faster rate than those of the treatment groups. Nevertheless, we performed an even more conservative sensitivity test by limiting the analysis to 7 years post-diagnosis. Only 30% of survival gains and 20% of the estimated option value accrued in the first 7 years after diagnosis. In this more conservative scenario the option value as a percentage of the survival gains from TKI treat-

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ments was reduced from 9% to 7%, given the limited time frame for the benefits from future medical breakthroughs to accrue.

Because option value captures the benefits from surviving long enough to take advantage of the next medical breakthrough, it is determined exclusively by the effectiveness of present and future treatments. In this regard, the greater option value of first-line treatment relative to second-line TKIs can be attributed largely to the substantial survival benefits of second-generation therapies. Several therapeutic approaches for a cure for CML are under evaluation,²⁴⁻²⁷ suggesting that actual innovation in second- and later-line CML treatment may develop faster than forecasted. In such a scenario, future research may provide a larger benefit from first- and second-line treatment than estimated here.

Given the available survival data for CML patients, this study, by necessity, focused on imatinib as the only first-line TKI treatment; however, both dasatinib and nilotinib have been found to offer better cytogenetic response than imatinib in recently completed trials,^{8,12,13,17} which points to greater survival gains.²⁸ Although our study did not directly quantify the option value of using second-generation TKIs in first-line treatment, based on the survival improvements relative to first-generation treatment that have been recently documented in the literature,^{8,12,13,17} we could expect larger option value from the newer TKIs if given as first-line therapy.

While the primary analysis used SEER data over the period 2000 to 2008, 2 sensitivity analyses reported in the eAppendix were used to determine whether CML-specific survival improved at an uncharacteristic rate over this period. Including patients diagnosed with CML as early as 1995 in the Cox proportional hazards regression provided quantitatively similar results and, subsequently, estimating option value at the lower and upper bounds of the survival forecasts' 95% confidence intervals also yielded similar results.

We also assessed the sensitivity of our option value estimates by varying the probability of first-line treatment failure over a wider spectrum than previously suggested.²⁰ Estimates were not overly sensitive to this key parameter, as the average option value for a recently diagnosed CML patient from future innovations in CML treatment ranged from 0.62 life-years (with a failure probability of 0.05) to 0.82 life-years (with a failure probability of 0.50) (see eAppendix).

While our analysis is tailored to the specific context of innovative TKI treatments for CML, our methodology also can be applied to other diseases. The feasibility of this method will naturally be favored in those areas for which comprehensive survival data are available (as is the case with SEER data in oncology). Although it is still possible to mea-

sure option value in disease areas for which survival data are scant but sufficient to identify treatment efficacy and post-treatment survival, such analyses will inevitably be subject to greater uncertainty.

Conclusion

Recent innovations in the treatment of CML have increased patient survival not only by improving the management of the disease, but also by allowing patients to live long enough to experience more effective future treatments. For a recently diagnosed CML patient, the option value of innovative therapies in terms of future medical innovations in CML and other diseases amounts to 0.76 life-years. This option value is equivalent to 9% of the average survival gains from existing treatments and is worth approximately \$63,000. Future innovations in CML treatment jointly account for 96% of this benefit.

Our study demonstrates to researchers and payers that, by ignoring option value, the traditional methods of health technology assessment undervalue life-extending health-care innovations, particularly those in areas of medicine in which rapid innovation is producing substantial survival gains. We provided methods for incorporating option value into standard health-technology assessment, and identified the scenarios for which this methodology could be applied in the future. It is worth noting that ongoing medical progress against a particular disease guarantees that the option value of available treatments will always be positive.

We have provided just 1 example of how option value could be applied in health technology assessment. While this study does not make any inference about the generalizability of the CML case to other therapies, the results underscore the need to account for option value in the assessment of health innovation, as failure to do so will likely result in the underestimation of overall value. Our framework is, however, applicable to various types of analyses, from survival benefits and cost-effectiveness analyses involving life-years or quality-adjusted life-years, to measures of an innovation's economic value. As medical progress continues to improve survival in a broad spectrum of disease areas, investigators performing future analyses may find the methodology developed in this study useful for calculating the option value of such innovations. Ultimately, a better understanding of the overall effectiveness of innovative treatments foreshadows significant improvements in the management of patient care.

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