The Value of Survival Gains in Myelodysplastic Syndromes

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ABSTRACT

OBJECTIVES: To measure the value of survival gains attributable to the introduction of 3 novel therapies for myelodysplastic syndromes (MDS).

STUDY DESIGN: Retrospective study of patients diagnosed with MDS in the Surveillance, Epidemiology and End Results Program (SEER) registry, clinical trial evidence for MDS therapies, and claims data.

METHODS: We used multivariate Cox proportional hazards models to estimate the increase in survival associated with the introduction of the 3 new therapies for patients diagnosed with MDS from 2001 to 2011 in the SEER cancer registry. Increases in survival associated with the 3 novel therapies were estimated using retrospective survival analyses and published clinical trial evidence. MDS treatment costs were estimated using Ingenix claims data and used to calculate the share of the value of survival gains retained by patients.

RESULTS: We estimated that the introduction of these 3 therapies is associated with a hazard ratio of 0.901 (P <.10), and a 73% increase in median survival from 33 to 57 months. We estimated that for current and future MDS patients, these 3 therapies will generate over $193 billion in cumulative value through extensions in patient survival.

CONCLUSIONS: This study demonstrates that the value of recently approved innovative therapies in MDS is large and that the value of survival gains in MDS far outweighs their costs.

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Over the past several decades, innovation in both the detection and treatment of cancer has resulted in improved survival rates.[1,2] Several tumor types—including breast,[3] colon,[4] chronic myeloid leukemia (CML),[5,6] multiple myeloma,[7] and non-Hodgkin lymphoma[8]—have experienced dramatic gains in survival, due in part to the introduction of targeted therapies, such as tyrosine kinase inhibitors (TKIs), vascular endothelial growth factor (VEGF) targeted drugs, immunomodulators (IMiDs), and proteasome inhibitors, among others.[9,10] In contrast to conventional chemotherapies that kill rapidly dividing cells—whether cancerous or not—targeted therapies inhibit cancer cell growth and improve survival by interfering with specific molecular targets.[11]

Several clinical trials investigating novel targeted therapies for myelodysplastic syndromes (MDS) have demonstrated improvement in overall survival (OS) and progression-free survival (PFS).[12,13] For example, azacitidine has been shown to successfully improve OS and quality of life,[14] increasing median OS by nearly 10 months, while reducing the risk of fatal complications.[13] Similarly, patients with MDS being treated with decitabine exhibited better overall response and PFS, and patients responsive to lenalidomide had a significantly lower risk of death or progression to acute myeloid leukemia (AML) after 6 months, compared with patients with MDS being treated with a placebo.[15-17]

The existing literature demonstrates that the return on investment in advances in treatments for cancer and acute myocardial infarction, among others, has been large, but may not be constant over time.[18-20] This study contributes to the larger debate surrounding the value of medical innovation and the need for studying value in specific disease, time, and geographic contexts, given ongoing movement toward linking reimbursement to value. The introduction of novel targeted therapies, in MDS and elsewhere, coincides with increased scrutiny toward the relative value and cost of cancer therapies more generally.[21-23] This attention motivates rigorous evaluation of the economic value of new cancer therapies, where value captures improved survival, improved

quality of life, reduced caregiver burden, as well as other dimensions of value.[24] In one recent analysis of CML, Yin et al (2012) measured the value generated by new novel targeted therapies along 1 dimension of value: survival gains. They estimated that the survival gains attributed to the introduction of TKIs generated significant social value.[25] Similarly, studies on the value of improvements in cancer survival and mortality find that these gains have significant societal value.[26,27]

TAKEAWAY POINTS

- Innovative treatments for myelodysplastic syndromes (MDS) have generated significant benefits for patients by markedly extending survival.
- The value of survival gains far outweighs their cost, suggesting that improving patient access to these MDS therapies is warranted.
- The value of survival gains represents a conservative estimate of the total value of innovative treatments for MDS to society, which also includes the value of medical cost offsets, productivity gains, and other sources of value, such as reduced caregiver burden.

For MDS, to our knowledge, there are currently no analyses that measure the value of survival gains attributable to innovative therapies relative to their cost.[28] Moreover, no study has measured MDS survival gains in the real world, where benefits may differ from those observed in clinical trials. This study addresses this gap in the literature. We estimated the value of survival gains in MDS from the introduction of 3 targeted therapies: azacitidine, decitabine, and lenalidomide. Following the analytical framework applied in Yin et al (2012),[25] this study used data from the Surveillance, Epidemiology, and End Results Program (SEER) cancer registry database for 2001 to 2011, to estimate survival gains in the real world as a result of the introduction of these 3 therapies. We then calibrated an existing economic model to value the estimated increases in survival.[29] Finally, we used the Ingenix Touchstone commercial claims database (Ingenix) to estimate treatment costs, which we compared with the total value of survival gains.

METHODS

Survival Analysis

We conducted 3 distinct subanalyses. In the first, we used SEER registry data from 2001 to 2011 for patients with MDS, and Cox proportional hazards models to estimate the increase in survival in the real world due to the introductions of key new therapies for MDS between 2001 and 2011. The primary independent variables in the survival models were the binary variables that indicated when new therapies were introduced (**Table 1**). Prior to 2001, the *International Classification of Disease* classified MDS as a blood disorder rather than a neoplasm, making the identification of MDS (diagnosed prior to 2001 in SEER) problematic. Therefore, we restricted our analysis to patients diagnosed in 2001 or later.

We included a binary independent variable—$YEARS_{2004\text{-}2005}$—that takes a value of 1 in (diagnosis) years 2004 and 2005, and another binary independent variable—$YEARS_{Post2006}$—that takes a value of 1 in years 2006 to 2011. The regression coefficient on $YEARS_{2004\text{-}2005}$ captures the survival effect of the introduction of azacitidine (introduced in 2004); and the coefficient on $YEARS_{Post2006}$ captures the effect of the introductions of lenalidomide (approved in late 2005) and decitabine (introduced in 2006), as well the availability of azacitidine. Because all 3 therapies have been available from 2006 on, we were only able to estimate the combined effect of the availability of all 3 therapies for MDS from 2006 to 2011. The hazard ratio (HR) associated with the $YEARS_{Post2006}$ variable is the primary estimate of the combined effect of new therapies on MDS survival, and is the key input into our economic model of the value of survival gains.

Importantly, in order to interpret the HR associated with the $YEARS_{Post2006}$ *as the combined effect of the 3 therapies*, we included a set of flexible time variables to capture the secular trends in survival that are unrelated to the introduction of azacitidine, lenalidomide, and decitabine. In this way, we would not confound the estimated impact of new therapies on survival with these unrelated changes in MDS survival. In our final specification, we included a cubic annual time trend. We also controlled for a rich set of patient demographic characteristics, including age at diagnosis, gender, tumor sequence, and race. This ensured that changes in survival due to changes in case mix over time would not be incorrectly attributed to the impact of new therapies for MDS.

Because SEER lacks information on which specific therapies patients utilize, the hazard model allowed us to estimate the average impact of new therapy introduction on the entire MDS population, including patients undergoing treatment with therapies other than azacitidine, lenalidomide, and decitabine. Hence, our regression estimates captured the "intended to treat" (ITT) effect of the 3 therapies on MDS survival. To estimate the survival impact on those treated by the new therapies (ie, the "treatment on the treated" (TOT) effect), we used the Ingenix claims data to calculate the average share of patients with MDS being treated by the new therapies between 2006 and 2011. We then scaled the ITT effect by the share of patients treated with the novel therapies to calculate the TOT effect.

TABLE 1. MDS Therapy Approval Dates

	FDA Approval Date
Azacitidine	May 19, 2004
Lenalidomide	December 27, 2005
Decitabine	May 2, 2006

MDS indicates myelodysplastic syndromes.

TABLE 2. Summary Statistics for MDS Patients[a]

	Diagnosed Before 2006	Diagnosed in 2006 or Later
Age at diagnosis	73.6 (12.52)	74.3[b] (12.36)
Female	46% (0.5)	44%[b] (0.5)
Married at diagnosis	51% (0.5)	51% (0.5)
Hispanic	7% (0.25)	7%[b] (0.26)
White	86% (0.34)	85%[b] (0.35)
Black	8% (0.27)	8% (0.27)
Asian/Pacific Islander	5% (0.23)	7%[b] (0.25)
Observations	15,235	22,790

MDS indicates myelodysplastic syndromes.
[a]Standard errors are in parentheses.
[b]Significant difference in mean patient characteristic pre- and post 2006.

Value of Survival Gains

To estimate the value of survival gains in MDS, we applied methods developed by Becker, Philipson and Soares (2005),[30] which allowed us to estimate the value patients place on increased longevity. This method involved calibrating an economic model to calculate the utility of patients with cancer when facing the baseline survival curve, as well as the utility curve when faced with an improved survival curve attributable to new treatments. This model also allowed us to estimate the dollar amount that would make baseline patients with cancer as well off as patients with the improved survival, holding all else equal. Following Becker, Philipson, and Soares (2005), we interpreted this dollar amount as the value of the survival gain.

Because utility in this framework depends on the value of consumption while alive, this dollar amount depends on patient income levels, which, at a very general level, dictates patients' ability to consume goods, including healthcare. The model was therefore calibrated to the income level of patients with cancer, in addition to discount rates, marginal utility of consumption, and other standard economic parameters, as summarized in Becker, Philipson, and Soares (2005) (see **eAppendix** for further details [available at **ajmc.com**]).[30]

The economic model takes as inputs the estimated survival gains, as well as patient "full" income levels, as the total value of time available for work and leisure.[31] We estimated patient income using the Medical Expenditure Panel Survey (MEPS) data from 2010 and 2011.[32] However, MEPS did not have a sufficient number of patients with MDS (who fall into the "other" cancer category) to allow for the estimation of tumor-specific estimates of income; therefore, to produce reliable estimates of annual income, we estimated the expected annual earnings and full income of all patients with cancer, 18 years or older, assuming earned income reflects 8 hours of work per day and, therefore, full income equals double earned income.

We estimated the annual treatment costs of these 3 therapies using claims data from the Ingenix database for years 2006 to 2012, averaging across years and inflating to 2013 dollars using the Bureau of Labor Statistics Consumer Price Index.[33] The Ingenix database is a private sector health insurance claims–based database that combines information from a wide array of different insurance providers. The database captures all healthcare claims, including prescription drugs, and inpatient, emergency, and ambulatory services for elderly and nonelderly individuals with employer-provided insurance from more than 50 large Fortune 500 firms. We calculated the present discounted value (PDV) of the increase in survival for a single patient over his or her lifetime, where value and costs in later years are weighted by each year's estimated survival probability. Finally, we calculated the PDV of the lifetime value and costs for all future patient cohorts.

The total PDV of the lifetime survival gains and costs considers future MDS incident cohorts together with the current cohort, assuming a 3% discount rate, and accounts for patent expiry: generic versions of azacitidine and decitabine became available in 2013, and the lenalidomide patent will expire in 2027. How much prices decline following patent expiry depends on several factors, including the number of generic manufacturers that enter the market, the complexity of producing the molecule, outpatient rather than pharmacy benefit coverage, branded-drug market share, the number of competing therapies, and the length of time since patent expiry.[34] For these reasons, the effect of patent expiry on the price of specialty drugs like oncologics may be different than the effect of expiry on nonspecialty drugs. To accommodate for this uncertainty in post patent expiry drug prices, we used a conservative estimate of the effect of patent expiration on drug prices. A recent study estimates that intravenously administered specialty drugs decline by 34% after patent expiry, and that oral specialty drugs decline by 21% after patent expiry.[34] We used these price declines when forecasting future costs of generic azacitidine, lenalidomide, and decitabine treatment in MDS.

RESULTS

Summary Statistics

The sample of patients diagnosed with MDS between 2001 and 2011 from the SEER cancer registry database contained 38,025 individuals. Descriptive statistics for the study sample are displayed in **Table 2**. Sixty percent of these patients were diagnosed in 2006 or later; patients diagnosed in 2006 or later were slightly older at diagnosis and less likely to be white, but overall, the 2 populations had very similar characteristics.

Change in MDS Survival Curves Attributable to New Therapies

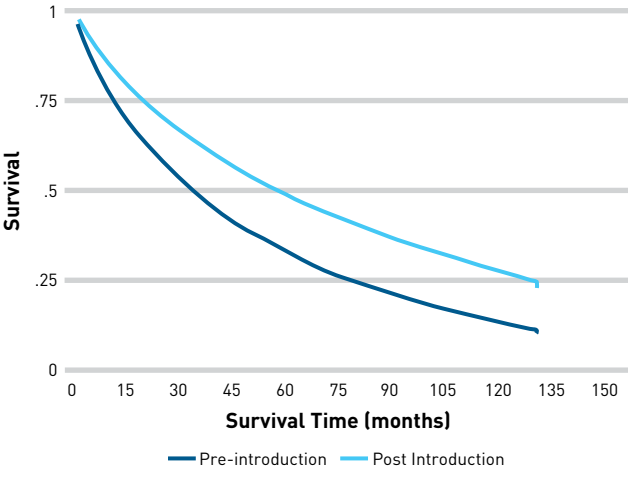
The coefficient on the post 2006 indicator reflected the decline in the hazard rate associated with the introduction of the 3 therapies relative to the hazard rate in years prior to their introduction (2001-2003). In our preferred model, which included more flex-

TABLE 3. Impact of Introduction of Novel MDS Therapies[a,b]

	(1)	(2)
HR associated with post 2006 = 1	0.891[c]	0.901[d]
SE	0.051	0.048
Linear annual time trend	X	
Cubic monthly time trend		X
Implied survival rate ratio (ITT)		1.07
Implied survival rate ratio (TOT)		1.28
Observations	38,025	38,025

HR indicates hazard ratio; ITT, intent to treat; MDS, myelodysplastic syndromes; SE, standard error; TOT, treatment on the treated; X, inclusion in the model.
[a]The table reports the HR associated with the post-2006 variable. Demographic controls include sex, age at diagnosis, marital status, race, and tumor sequence.
[b]The model in column (1) includes a linear annual time trend and the model reported in column (2) includes a cubic month-of-diagnosis time trend as controls for secular time trends in survival.
[c]Indicates significance at the 95% level.
[d]Indicates significance at the 90% level.

FIGURE. Estimated Survival Curves for MDS Patients Pre- and Post Introduction[a,b]



[a]New treatments include azacitadine (2004), decitabine (2005), and lenalidomide (2006).
[b]Model includes controls for age, sex, race, time trends, and tumor sequence.
Sources: 2001-2011 Surveillance, Epidemiology and End Results registry data.

ible controls for secular trends in survival, we estimated that the introduction of these 3 therapies is associated with an HR of 0.901 ($P < .10$; see column 2 of Table 3). That is, we estimated that patients with MDS diagnosed in 2006 or later had an approximately 10% lower chance of dying within the year (conditional on surviving to that year) than patients diagnosed in 2006, but under the counterfactual that the 3 new therapies were not introduced (Table 3). Note that the counterfactual survival rate in 2006 is the estimated survival rate in the pre-introduction (2003) period, adjusted for the secular increase in survival between 2003 and 2006.

Approximately one-fourth of patients with MDS had claims for at least 1 of the 3 novel treatments consistently over this period, resulting in an overall average increase from 33 to 57.5 months in median survival for treated individuals (Figure).

Societal Value of Survival Gains Attributable to New Therapies

The annual value of survival gains associated with innovative treatments—roughly $208,000 per year—equals the estimated amount a patient would pay for the higher survival profile associated with the new therapies. Note that this is conservative compared with the value of a 24-month (from 33 to 57.5 months) increase in median survival, as implied by conventional health technology assessment methods, which would range from $400,000 to $600,000 depending on the assumed valued of a statistical life-year.[35] These differences stem from diminishing utility in longevity, which appeared in the model in 2 places: 1) the size of the survival gain and 2) the baseline survival prior to the introduction of the new therapies. If either of these are small, the marginal utility, and hence, valuation, of an incremental survival gain is larger than for the same incremental survival when the gain is large or when the baseline survival is already large.

Table 4 compares the estimated value of survival gains to costs, where the annual treatment costs of the new therapies, from 2006 to 2012, were estimated using Ingenix. The value of survival gains were estimated to exceed the cost of therapy, with an annual and lifetime net benefit to patients of $68,500 (column 1) and $130,100 (column

TABLE 4. Value of Survival Gain for Patients With MDS[a,b]

	Annual Value per Patient (1)	Lifetime Present Value per Patient (2)	Lifetime Value for a Single Cohort of Patients (3)	PDV of Lifetime Value for All Current and Future Cohorts (4)
Value of survival gain	$208,000	$395,200	$5.8 billion	$192.9 billion
Cost	$139,500	$265,100	$3.9billion	$108.8 billion
Patient net benefit	$68,500	$130,100	$1.9 billion	$84.2 billion

MDS indicates myelodysplastic syndromes, PDV indicates present discounted value.
[a]All values reported in 2013$.
[b]Column (1) reports the per-patient annual value, cost, and net benefit of treatment to patients. Column (2) reports the PDV over the incremental gain in patients' life expectancy (estimated at 1.9 years on average).[6] Column (3) reports the lifetime value for a single cohort of patients. Column (4) reports PDV lifetime value for all current and future incident cohorts. We estimate the incidence cohort size is 14,650, and assume a 3% annual discount rate.

2), respectively. Assuming an incidence of 14,650 new patients with MDS per year, we estimated the annual net value to a single cohort of patients with MDS equals $1.9 billion (column 3). We estimated the number of new cases per year at 14,650 based on an incidence rate of 4.7 per 100,000 population[36] and a population size of 311,592,000 in 2011.[37] The cumulative PDV of the lifetime survival gains of $193 billion for all future cohorts far exceed the costs, resulting in positive net benefits of $84 billion for patients with MDS (column 4).

DISCUSSION

In this study, we measured the value of survival gains in MDS, for patients diagnosed in 2006 or later, as a result of treatment with 3 new targeted therapies: azacitidine, decitabine, and lenalidomide. As no other drugs have been approved for MDS since 2006 and no other major advances in the diagnosis or treatment of MDS were made in the study period (ie, 2001-2011),[38] we can be reasonably confident that our survival model accurately captures the impact of the introduction of these 3 therapies on survival. Our Cox proportional hazards model estimated the shift in the probability of survival associated with the introduction of these 3 novel therapies while controlling for secular time trends and patient characteristics. We estimated that the introduction of these 3 therapies would be associated with an HR of 0.901. Given the pre-introduction survival curve, this translates to an increase in median survival of 74%, from 33 months to 57.5 months. The estimated ratio of median survival in the post period to median survival in the pre-period, observed in the real world, align well with the clinical trial results, as it landed between ratios of median OS, 1-year survival, and PFS in the treatment and control groups from clinical trials for azacitidine, lenalidomide, and decitabine.[13,14,16,17] Fenaux et al (2009) found a median OS ratio of 1.6 (24/15) in high-risk patients with MDS treated with azacitidine versus conventional care (ie, best supportive care, low-dose cytarabine, or intensive chemotherapy). Silverman et al (2002) also found an OS ratio of 1.6 (18/11) comparing azacitadine plus supportive care to supportive care alone. Comparing decitabine and supportive care, Lübbert et al (2011) found decitabine nearly doubled 1-year PFS in intermediate and high-risk elderly patients with MDS.

The calibrated economic model developed by Becker, Philipson, and Soares (2005) allowed us to calculate the amount that patients with cancer would pay for discrete increases in the probability of survival, as associated with the increase in survival estimated in the SEER data. We estimated that the cumulative value of survival gains would be large—$193 billion—and exceed the cost of therapy by $84 billion. This estimate is conservative compared with conventional health technology assessment methods.

Strengths and Limitations

This study has several strengths. First, we used rigorous methods to estimate gains in survival in the real-world setting, as opposed to a small trial sample, using the SEER registry database. SEER is the most comprehensive and detailed data on cancer incidence and survival in the United States available. Second, we used a sound economic framework for valuing survival gains. Finally, we had a relatively large sample size in the SEER cancer registry data to detect significant and meaningful survival gains.

This study has some limitations, however. The SEER data are not nationally representative and do not include information on the specific treatments utilized by patients with cancer. We addressed this limitation by estimating therapy utilization in the real world with the Ingenix claims data. Additionally, the coding, diagnosis, and definition of MDS have changed considerably over the past 40 years.[39] Specific and consistent *International Classification of Disease for Oncology, 3rd Edition*, coding for MDS first became available in SEER starting in 2001. Thus, we only used data from 2001 to 2011, and had a 3-year window prior to the introduction of azacitidine to estimate the survival gains in MDS. Lastly, our estimated value of novel treatments for MDS are underestimates to the extent that new treatments decrease the indirect costs of treatment (ie, productivity losses and caregiver burden). Novel treatments that have fewer side effects, are oral rather than intravenous, or that have to be taken less frequently, for example, may also decrease the indirect costs of treatment.

Another study limitation is that the Ingenix Touchstone claims database is not nationally representative, either. However, the database is among the largest commercial claims databases. Moreover, the large size and broad representation of the database is necessary for us to estimate the cost of physician-administered therapies for a relatively small indication in MDS.

CONCLUSIONS

This study demonstrates that the value of recent innovative therapies in MDS is large. Moreover, the value of survival gains far outweighs their cost, suggesting that improving patient access to these therapies in MDS is warranted. More generally, this study highlights the importance of economic evaluation in informing payers, policy makers, and other stakeholders about the economic value of novel therapies, and the benefits they provide to patients and society. ■

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eAppendix

We used an economic model developed by Becker, Philipson, and Soares (2005)[1] to calculate the social value of survival gains attributable to the introduction of 3 novel therapies for MDS. This economic framework calculates patients' willingness-to-pay for extensions in life expectancy and captures discrete (rather than marginal) increases the probability of survival. In this study the utility of myelodysplastic syndromes (MDS) patients was calculated given the survival curve in the post-2006 time window and the average income level among cancer patients.

Cancer patient income was estimated using the 2010–2013 Medical Expenditure Panels Study. We calculated the amount of additional annual income patients would need to reach the same level of utility given the pre-2006 survival curve and interpret this amount as the annual value of the improved survival profile associated with the introduction of 3 novel therapies for MDS.

To calculate the lifetime value within an annual cohort of MDS patients we multiplied the lifetime individual MDS patient values by the annual MDS incidence. We then calculated the net present value (NPV) of the lifetime values across all present and future cohorts to determine the total social value of survival gains associated with novel treatments for MDS. The estimated social value of novel treatments for MDS introduced in 2004–2006 to all future cohorts was discounted at 3% per annum based on the precedent in the health economics literature.

eAPPENDIX REFERENCE

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