



Linda Holmes. *Marine Street*. Oil on canvas, 22" × 28".

Research suggests that oral lenalidomide is a cost-effective treatment for transfusion-dependent, low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality.

Cost Effectiveness of Lenalidomide in the Treatment of Transfusion-Dependent Myelodysplastic Syndromes in the United States

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Lenalidomide has been approved for the treatment of transfusion-dependent low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a chromosome 5q deletion with or without additional cytogenetic abnormalities. We evaluated the cost effectiveness of lenalidomide versus best supportive care (BSC) in these patients. We developed a decision analytic model to compare costs and outcomes of lenalidomide with BSC without recombinant erythropoietin (EPO) versus BSC with EPO over 1 year. Outcome measures were transfusion independence and quality-adjusted life years (QALYs) gained. The model incorporated costs of medications, transfusions, chelation, laboratory tests, office visits, and other resources associated with each therapy. Lenalidomide therapy was associated with an estimated incremental 0.53 transfusion-free and 0.25 QALY gain compared to BSC at 1 year. The costs of lenalidomide therapy were substantially offset by reduced blood transfusion and EPO costs. One-year total treatment costs were estimated at \$63,385 for lenalidomide and \$54,940 for BSC. The incremental cost-effectiveness ratio for lenalidomide vs BSC was estimated at \$16,066 per transfusion-free year and \$35,050 per QALY gained, values within the acceptable cost-effectiveness ranges for a new therapy. Results suggest that oral lenalidomide is cost effective in the United States in the treatment of transfusion-dependent, low- or intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality. Confirmation of these findings awaits results of an ongoing randomized phase III trial (MDS-004 study).

Introduction

Effective treatment for patients with International Prognostic Scoring System (IPSS) low- or intermediate-1 risk myelodysplastic syndromes (MDS) and transfusion-dependent anemia is limited, often resulting in reliance on red blood cell (RBC) transfusions and iron chelation therapy. Transfusion dependency has been associated with a significant negative impact on quality of life (QOL), poorer survival,^{1,3} and higher health care costs.⁴

Lenalidomide, a new immunomodulatory drug, received fast-track designation and was approved by the US Food and Drug Administration (FDA) for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. (Lenalidomide in combination with dexamethasone was also approved by the FDA in June 2006 for the treatment of patients with multiple myeloma who have received at least one prior therapy.) Clinical trials have shown that lenalidomide leads to hematologic improvement characterized by sustained elevation in hemoglobin (Hgb) values, histologic improvement, and cytogenetic normalization, which manifest clinically as transfusion independence.^{5,6}

In addition to convincing safety and efficacy data, there is an increasing demand for cost-effectiveness data for new therapeutic interventions. Across the globe, health care payers consider health economic data when evaluating new drugs, which in turn influences patients' access to medical care. For example, in the United States, the Academy of Managed Care Pharmacy (AMCP) has recently issued updated guidelines for submitting information on products to formulary committees, including data on their cost effectiveness.⁷

The objective of this analysis was to evaluate the cost effectiveness of lenalidomide treatment for transfusion-dependent patients with MDS compared to the current standard of care in the United States. We applied decision analytic modeling to combine best available evidence on effectiveness and medical resource utilization (MRU) using multiple data sources. This approach enabled us to provide an estimate of the likely cost effectiveness of lenalidomide, which is informative for health care payers and other health professionals in the United States.

Methods

A decision analytic model was developed in Excel® (Microsoft Corp, Redmond, Wash) to evaluate and compare the health benefits and costs associated with lenalidomide. The model incorporates clinical data for lenalidomide from the pivotal multicenter phase II study and combines data from other information sources on efficacy, safety, and health care utilization.

The therapeutic options we evaluated in the model included (1) lenalidomide therapy, including best supportive care (BSC) elements but excluding the use of erythropoietin (EPO) (lenalidomide group), with cost comparison to (2) BSC with blood transfusions and recombinant hematopoietic growth factors, including EPO (BSC group).

The model compared patients with transfusion-dependent MDS currently on BSC therapy over a 1-year period after initiating new treatment with those receiving lenalidomide. Treatment outcomes were characterized as transfusion independence, reduced transfusion independence (a 50% or greater reduction in transfusion requirement), or persistent transfusion dependence. Based on response rate, time to transfusion independence, and duration of transfusion independence, the model calculated the estimated time patients spend in these health states. The model also assigned QOL weights to the transfusion health states, and as such calculated quality-adjusted life years (QALYs) in each group. Finally, the model estimated MRU and annual direct medical costs associated with each treatment option and expressed cost effectiveness in terms of costs per transfusion-independent year gained and per QALY gained. Table 1 provides a condensed overview of key model characteristics.

Clinical Data Sources and Assumptions

Rate and duration of transfusion independence and blood transfusion requirements before and after the lenalidomide were estimated from results of the multicenter phase II clinical trial (MDS-003; N = 148). Patients enrolled in the study had transfusion-dependent MDS and received standard BSC, including granulocyte colony-stimulating factor (G-CSF) treatment, but they did not receive EPO.⁶ Data for BSC were com-

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Abbreviations used in this paper: MDS = myelodysplastic syndromes, EPO = erythropoietin, BSC = best supportive care, QOL = quality of life, QALY = quality-adjusted life year, RBC = red blood cell, MRU = medical resource utilization, G-CSF = granulocyte colony-stimulating factor.

bined from the “Nordic MDS Group” trials that included transfusion-dependent MDS patients (efficacy and transfusion requirements)⁸ and the placebo arm of a randomized phase III placebo-controlled MDS trial (safety) (THAL-001 study).

The efficacy data was adjusted to account for differences in patient characteristics between the MDS-003 and the “Nordic cohort” with respect to transfusion-dependency status, IPSS score (patients with IPSS low or intermediate-1 risk score were included), and prior history of EPO response. The adjustment for prior EPO history involved the assumption that the same proportion of patients who had previously failed EPO in the lenalidomide group would not become transfusion-independent in the BSC with EPO group. The model did not adjust for

any potential differences in efficacy outcomes in the BSC arm by cytogenetic characteristics due to the small number of patients with deletion 5q status (N = 11) in the “Nordic cohort.” Table 2 summarizes baseline patient characteristics in each group before any adjustments for differences in prior history of EPO use were made.

The model also includes estimates for the frequency of important complications due to treatment or underlying disease such as thrombocytopenia and granulocytopenia (neutropenia, leukopenia). However, RBC transfusion-related complication rates, such as reactions, infections, and long-term complications due to iron overload, were not incorporated in the model due to the short time horizon and lack of data in MDS subpopulations.

Table 1. — Model Framework

Comparators	Lenalidomide vs BSC
Patient Population	MDS patients with RBC transfusion-dependent low- or intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities
Time Horizon	1 year
Perspective	Health care payers in the United States
Medical Resource Utilization and Costs	Primary intervention drugs, blood transfusions, administration of drugs and transfusions, adverse events, and other standard of care medical costs
Currency	\$ US
Effectiveness Measures	Transfusion-independent time gained; QALYs gained
Type of Analysis	Cost-effectiveness analysis and cost-utility analysis
Data Sources	<ul style="list-style-type: none"> • Lenalidomide clinical trials; MDS-003 trial • Published literature (medical, epidemiology, economic literature) • Patient interviews • Treatment guidelines and local expert opinion • Additional information sources on unit costs (eg, Redbook, Medicare fee schedules, and hospital data)

Table 2. — Summary of the Clinical Data Sources

	Lenalidomide	BSC
Study Design	Phase II clinical trial (MDS-003) ⁶	Observational cohort study (Nordic study) ⁸
No. of Patients	148	61
EPO History	73% of patients had failed prior EPO treatment prior to enrolling in the trial.	Patients had no prior EPO use.
Therapy	Patients started treatment with a lenalidomide dose of 10 mg either daily or for 21 days every 4 weeks. Dose was reduced to 5 mg daily in the majority of patients during the course of treatment.	The standard weekly maintenance dose was 35,000 IU EPO and 375 µg G-CSF.
Response Rate	Transfusion independence was observed in 67% of patients treated with lenalidomide.	Transfusion-independence was observed in 33% of transfusion-dependent MDS patients.
Duration of Response	Time to transfusion independence was 4.6 weeks. The median duration of transfusion independence was not reached at 1 year in responding patients (62 of 99 transfusion-independent responders have remained transfusion independent for at least 52 weeks as of a data cutoff of September 1, 2005).	Time to transfusion independence was 2.3 weeks. The median duration of response was not reached at 1 year in responding patients (the median duration of transfusion independence was 23 months among responders).

Assessment of Quality of Life

In order to elicit the value of transfusion independence and reduced transfusion burden compared with transfusion dependence, we conducted health utility interviews with a group of MDS patients in the United States (N = 8). Health state descriptions were developed based on published literature and reports from MDS patient focus group discussions. Each health state card included different severity/intensity of problems on the following key QOL domains:

- Reliance on blood transfusions; time spent on transfusions; and dependence on availability and accessibility of health care provider facility.
- The need to arrange one's life around medical appointments.
- Fatigue and tiredness that limits performance of routine physical activities.
- Disease interference with social functioning and family life.
- Worry about the future due to health condition.
- Discomfort associated with health condition and its treatment; feeling of being at risk for infections.
- Reliance on family or other caregiver support in taking care of oneself and routine activities; feeling of being a burden to family due to health condition.
- Feeling sad, hopeless, and helpless because of health condition.

Face-to-face interviews used the time trade-off (TTO) method⁹ to value the health states on a scale anchored on 1 (perfect health) and 0 (dead). The utility results were incorporated into the model as a QOL adjustment of time spent in transfusion independence, reduced requirements, and transfusion dependency.

Medical Resource Utilization

The model incorporated medical resources such as drugs, transfusions, laboratory tests, office visits and other health care resources. The pretreatment annual transfusion requirement was assumed to be the same: 15 transfusions with an average of 2 units/transfusion (ie, 30 units of RBCs) in both treatment arms of the model based on the MDS-003 trial data. The model assumed that a transfusion included 2 units of RBCs and 0.18 units of platelets during treatment based on MDS-003 data. Estimates for the utilization of iron chelation treatment by transfusion-dependency status were taken from the MDS-003 study and the proportions were applied in each arm of the model (21% utilization rate among those who became transfusion independent and 98% utilization rate among transfusion-dependent patients).

Data on lenalidomide utilization were taken directly from the MDS-003 trial. Within a 1-year follow-up period, the mean per-patient utilization of lenalidomide was 123 doses of 5-mg capsules and 81 doses of 10-mg

Table 3. — Key Medical Resource Items and Their Unit Costs*

Primary Drug Intervention (85% of average wholesale price)		
Revlimid®, 5 mg	\$223	ReadyPrice® 2006
Revlimid®, 10 mg	\$232	ReadyPrice® 2006
EPO, 40,000 IU	\$406	ReadyPrice® 2005
G-CSF, 300 µg	\$187	ReadyPrice® 2005
Outpatient Services		
Physician office visit	\$83	Medicare Physician Fee Schedule
Subcutaneous injection	\$19	Medicare Physician Fee Schedule
Transfusion-Related Costs		
Average RBCs, each unit	\$201	Medicare Hospital OPPS
Platelets, each unit	\$48	Medicare Physician Fee Schedule
Transfusion of blood or blood components	\$215	Medicare Physician Fee Schedule
Transfusion-related laboratory tests:		
Compatibility tests, each unit	\$20	Medicare Hospital OPPS Final Rule 2005
Irradiation of blood, each unit	\$20	Medicare Hospital OPPS Final Rule 2005
Pooling of platelets or other blood	\$20	Medicare Hospital OPPS Final Rule 2005
Fresh frozen plasma, thawing, each unit	\$20	Medicare Hospital OPPS Final Rule 2005
Comprehensive metabolic panel	\$15	2005 Clinical Laboratory Fee Schedule
Complete blood count, automated	\$11	2005 Clinical Laboratory Fee Schedule
Iron chelation therapy, 500 mg deferoxamine mesylate	\$15	ReadyPrice® 2005
Adverse Events and Disease Complication Related Costs		
Thrombocytopenia		
Granulocytopenia (including neutropenia and leucopenia)	\$7,100	Medicare Hospital IPPS Final Rule 2005
	\$7,200	Medicare IPPS Final Rule 2005
IPPS = inpatient prospective payment system		
OPPS = outpatient prospective payment system		
* As lenalidomide was FDA-approved in December 2005, the ready-priced software (ReadyPrice®, Thomson Micromedex, Greenwood Village, Colo) was accessed in January 2006 to estimate average wholesale price.		

Table 4. — Cost-Effectiveness Results From Base-Case Analysis

	Lenalidomide	BSC
Health Outcomes		
Transfusion-free patients	67%	8.9%
Time to response in responders	4.6 weeks	2.3 weeks
Duration of response in responders (within 1 year)	47.4 weeks	49.7 weeks
Transfusion-free year	0.61	0.08
QALY	0.78	0.53
Costs		
Annual cost of primary intervention regimens	\$52,596	\$36,196
Annual cost of transfusions	\$7,574	\$18,101
Annual cost of drug-related complications	\$3,215	\$643
Total annual treatment cost	\$63,385	\$54,940
Cost Effectiveness		
Incremental cost per transfusion-free year gained	\$16,066 per transfusion-free year	
Incremental cost per QALY gained	\$35,050 per QALY	

capsules. Twenty-three percent of patients in the MDS-003 trial also received G-CSF therapy. Utilization of EPO and G-CSF treatment in the BSC group was taken from the “Nordic study” (weekly mean dose of 35,000 IU EPO and 375 µg G-CSF) but were slightly modified in the model calculation to reflect the standard US practice (weekly dose of 40,000 IU EPO and 300 µg G-CSF). The model also assumed, according to standard US practice in this patient population, that all patients receive EPO treatment as part of their care even if they do not become transfusion-independent.

The model also incorporated other direct medical costs related to medications and their monitoring. Monitoring visits related to lenalidomide treatment during the first year, included weekly visits for 8 weeks (8 visits), biweekly visits for the second 8 weeks (4 visits), and monthly visits for the remaining year (8 visits). In addition, transfusion-related medical resources (eg, blood components, iron chelation therapy, laboratory procedures, and administration of transfusions) as well as diagnostic tests, office visits, and other medical resource use also were captured in the model. The utilization of other medical resources was estimated based on clinical recommendations and expert opinion.

Unit Costs

We used sources for unit cost information that are widely applied in cost-effectiveness analyses in the United States. Estimates for drug costs were based on discounted published average wholesale price, and estimates for other direct medical costs used Medicare fee schedules that represent a reasonable proxy for provider costs. The key medical resource use items, their unit cost, and source of information are summarized in Table 3. All costs were expressed in 2005 US dollars.

Cost Effectiveness and Sensitivity Analysis Methods

Mean health benefits, annual treatment costs, the incremental cost per transfusion-free year gained, and the

incremental cost per QALY gained with lenalidomide vs BSC were estimated in a base-case analysis. Uncertainty surrounding the base-case estimates was tested to evaluate the impact of varying certain key parameter estimates over a range of plausible values. One-way sensitivity analyses were performed to test assumptions on key model parameter estimates within reasonable ranges of assumptions. Multi-way probabilistic sensitivity analyses using Monte Carlo simulation techniques with Crystal Ball® software (Decisioneering Inc, Denver, Colo) were undertaken to

incorporate likely distributional characteristics of key model parameters and to calculate the cost-effectiveness acceptability curve. This method is typically used in cost-effectiveness analyses when the uncertainty around the overall cost-effectiveness ratio is explored, instead of reporting statistical significance separately for each efficacy outcome and for costs.^{7,10,11}

Results

Base-Case Cost-Effectiveness Analysis Results

Table 4 provides a summary of key clinical results on health outcomes, per-patient treatment costs, and cost effectiveness. Based on the results of the phase II efficacy study and the base-case model calculations, we observed that lenalidomide leads to longer transfusion-independent time compared to BSC and EPO plus G-

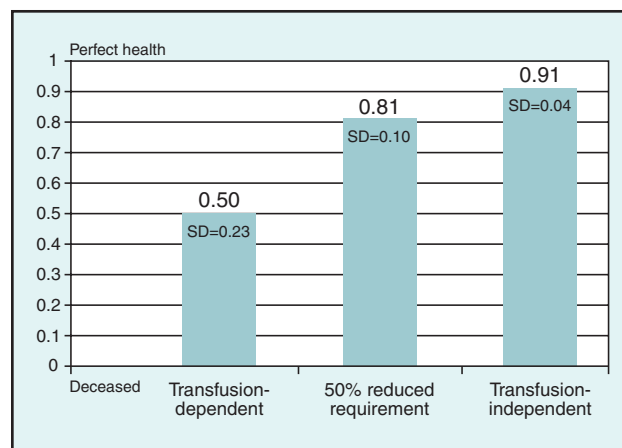


Fig 1. — Patients' valuation of health states associated with transfusion-dependence and transfusion-independence. This figure illustrates how MDS patients (N = 8) from an independent interview survey valued health states associated with being transfusion dependent and transfusion independent. The interview used the so-called time trade-off (TTO) method to value the health states on a scale anchored on 1 (perfect health) and 0 (dead). Higher ratings represent better health states. These ratings, also called “health utilities,” were used in the cost-effectiveness model as a quality adjustment to calculate QALYs in each arm of the model.

CSF treatment. After adjusting for differences in patient characteristics across the MDS-003 and the “Nordic study,” the mean transfusion-free time within the 1-year time horizon of the model was 0.61 vs 0.08 year in the lenalidomide and the BSC groups, respectively. This difference was primarily due to the higher transfusion-independence rate observed with lenalidomide. The median duration of transfusion independence among responders lasted for 1 year in both groups after excluding assessments beyond the 1-year time frame of the model.

Health utility interviews revealed that MDS patients valued transfusion independence as a significantly better health state compared to living with transfusion dependence (0.91 vs 0.50 health utility scores, respectively) (Fig 1).

After weighting time spent in transfusion-dependent and -independent health states with patients’ valuations of these health states, the model showed that the mean QALY was higher in the lenalidomide group compared with the BSC group (0.78 vs 0.53 QALY, respectively).

Cytopenic complications due to disease or the underlying condition was higher in the lenalidomide group compared with the BSC group, with rate of grade III/IV thrombocytopenia of 52% vs 8.3%, and grade III/IV granulocytopenia (neutropenia, leukopenia) of 57.4% vs 14.6%, respectively. As reported in the MDS-003 trial, the majority of adverse events (greater than 90%) in the lenalidomide group were observed within

the first 3 months of therapy and were manageable through dose reductions and supportive care. Thus, we programmed the model to account for these types of dosage adjustments and their subsequent impact on adverse events, clinical outcomes, and costs.

The model demonstrated that RBC transfusion requirements were 62% lower in the lenalidomide group compared with the BSC group in the first year. The costs of lenalidomide therapy were largely offset by reduced blood transfusion and EPO costs. One-year total treatment costs were estimated at \$63,385 for lenalidomide vs \$54,940 for the BSC regimens.

In summary, lenalidomide therapy led to an estimated 0.53 transfusion-free year and 0.25 QALY gain compared to BSC at 1 year at an estimated annual additional cost of \$8,445. These results translate into an incremental cost-effectiveness ratio of \$16,066 per transfusion-free year gained and \$35,050 per QALY gained for lenalidomide vs BSC in the base-case analysis.

Sensitivity Analyses

A series of one-way sensitivity analyses tested assumptions on pretreatment transfusion requirement, health utility associated with transfusion independence, transfusion independence rate with EPO, and transfusion independence rate with lenalidomide. Fig 2 illustrates the results in a tornado diagram. The incremental cost-effectiveness ratio for lenalidomide vs BSC varied between \$13,798 and \$18,672 per transfusion-inde-

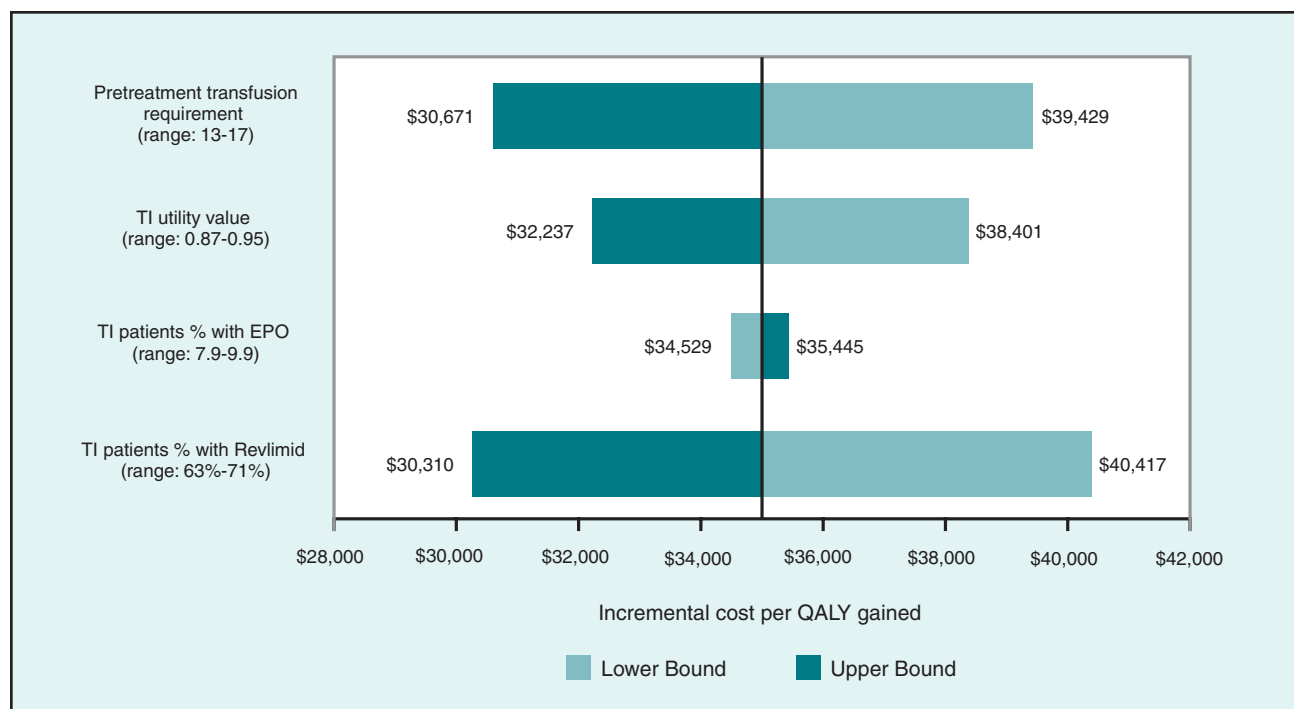


Fig 2. — One-way sensitivity analyses: incremental cost effectiveness of lenalidomide vs BSC (\$/QALY). Base-case analysis results assumed pretreatment transfusion requirement: 15; utility associated with transfusion independence: 0.91; transfusion-independent patients with EPO: 8.9%; transfusion-independent patients with lenalidomide (67%). The incremental cost-effectiveness ratio in the base-case analysis was \$35,050 per QALY gained. This figure shows the impact of changes in base-case assumptions on the cost-effectiveness ratio. Each of the four sensitivity analyses was run independently, assuming that all other variables were constant in the model.

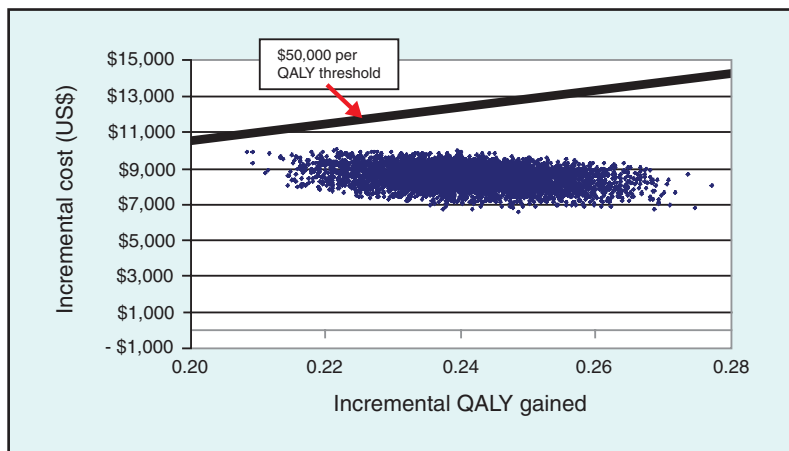


Fig 3. — Multi-way probabilistic sensitivity analysis. This figure illustrates the results of a multi-way probabilistic sensitivity analysis in which the model simulated random health and economic outcomes based on ranges of assumptions on various model parameters and their distributional characteristics, including pretreatment transfusion requirements, transfusion-independence rate with lenalidomide and BSC, and health utility values associated with achieving transfusion independence. Each dot represents a patient pair on lenalidomide and BSC treatment, showing the additional QALY gained value and the additional total treatment cost with lenalidomide. Those results located under the \$50,000 cost-per-QALY threshold line show cases when a unit of QALY gain was achieved under \$50,000 incremental cost.

pendent year gained and \$30,310 to \$40,417 per QALY gained, suggesting acceptable ranges of cost effectiveness for a new therapy.

The impact of the potential for lenalidomide wastage associated with dosage reduction was also tested in one-way sensitivity analysis. Wastage may occur in the real-world setting when a patient is switched to a reduced lenalidomide dosage due to an adverse event or toxicity, and the remaining capsules from the initial higher dosage, although dispensed, will not be taken and will be replaced by a lower dosage when treatment is continued. The incremental cost-effectiveness ratio varied between \$40,410/QALY and \$51,130/QALY as the model assumed an average number of wasted capsules per patient between 7 and 21. Thus, even when real-world wastage is considered, lenalidomide remains cost effective.

Fig 3 illustrates the result of a multi-way probabilistic sensitivity analysis that simulated and followed a cohort of 5,000 pairs of patients receiving lenalidomide or BSC therapy after entering the model. The simulation assumed lognormal distribution of transfusion requirements and triangular distribution of all other variables. Each dot of the figure represents the incremental health benefit (QALY) and the incremental treatment cost observed between the patient pair receiving lenalidomide vs BSC therapy. The analysis confirms that in the majority of cases, patients on lenalidomide therapy achieved a positive health benefit at an additional cost compared to BSC. Cases under the \$50,000/QALY line achieved the incremental health benefit at a “reasonable” additional cost, when “reason-

able” is defined as a unit of QALY gain at less than \$50,000 extra cost.

Fig 4 shows the proportion of cases (ie, the probability of) achieving a unit of health gain at an additional cost of less than a defined “reasonable” threshold value, assuming various ranges for cost-per-QALY thresholds that health care payers are willing to pay for a unit of QALY gain. The higher the threshold value that health care payers are willing to pay, the higher the chance is that the treatment will be regarded as cost effective. The analysis confirmed that the lenalidomide strategy was more likely to be cost effective than BSC when a cost-per-QALY threshold of over \$35,000 is considered. The figure also characterizes the probability of lenalidomide being cost effective at different cost-effectiveness thresholds.

Discussion

We report a new economic modeling framework to compare the cost effectiveness of lenalidomide vs BSC in patients with transfusion-dependent, low- or intermediate-1-risk MDS associated with a chromosome 5q deletion treated in the United States. Results from the model show that lenalidomide is a cost-effective treatment in these patients, owing to its improved efficacy in this cytogenetic subgroup, oral route of administration, reduced RBC transfusion and EPO requirements, and ability to provide patients with the benefits associated with transfusion-free living.

The economic literature in MDS is limited, and hence there is a paucity of comparative data evaluating the cost effectiveness of other currently available MDS treatments. Based on our literature review, we are

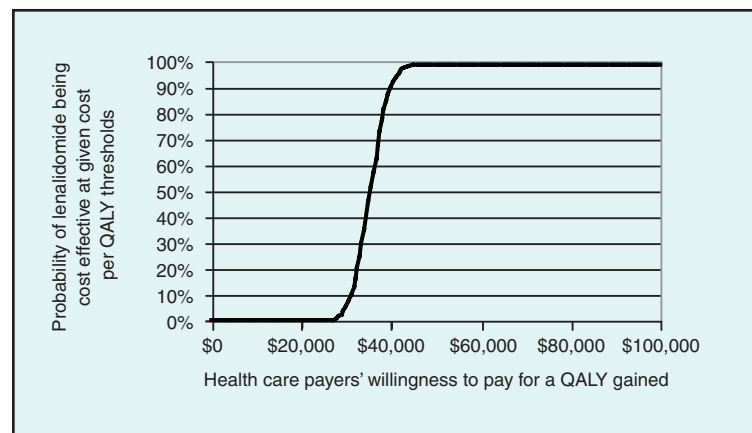


Fig 4. — Cost-effectiveness acceptability curve. This figure illustrates the probability that lenalidomide strategy is cost effective over BSC given different threshold values that health care payers are willing to pay for a QALY gained.

aware of only four other published studies on the cost of MDS treatment.^{4,12-14} The most relevant data on the treatment cost of transfusion-dependent MDS patients is from a claims data analysis from the United States.⁴ This study reported that the mean treatment cost of transfusion-dependent MDS patients was over \$58,000 per year. This overall finding is consistent with results on total treatment cost with lenalidomide and BSC; however, Frytak et al⁴ estimated a higher cost for inpatient care than we included in the model. This may be due to differences in the patient population, the model assumptions that all transfusions were administered in the outpatient setting, and the fact that the Frytak study included additional treatment of comorbidities related or unrelated to blood transfusions.

Comparable MDS cost-effectiveness data also are lacking, compounded by limited information on the cost effectiveness of similar technologies in rare patient populations. We are aware of one study that reported cost-per-QALY ratios that may be relevant for the interpretation of our cost-effectiveness analysis. A study that compared EPO to RBC transfusions in patients with anemia induced by radiotherapy or chemotherapy (including some MDS patients) found that the cost-effectiveness ratio ranged between \$110,769 to \$214,391 per QALY.¹⁵

It is important to note that according to widely quoted thresholds for “socially acceptable” cost-effective care, a cost-per-QALY ratio less than \$50,000 suggests that the therapy is cost effective; a range between \$50,000 and \$100,000 suggests that the technology warrants consideration for adoption and diffusion; while a value over \$100,000 suggests that the technology is generally not considered cost effective.¹⁶ In addition, there is an ongoing debate about whether the cost-effectiveness threshold for medications for orphan diseases should be higher or similar compared with those indicated for more prevalent diseases.^{17,18} Given these considerations and the unmet medical needs anticipated for transfusion-dependent MDS, we believe that lenalidomide is within the “acceptable” threshold.

In the absence of head-to-head economic studies of lenalidomide or other MDS therapies, the economic modeling analysis reported here provides a relevant framework within which MDS treatment costs and health gains can be studied. The model structure reflects current treatment patterns in the United States, uses efficacy data from best available studies of transfusion-dependent MDS patients, incorporates the views of United States MDS patient representatives, and calculates cost effectiveness based on standardized United States cost estimates.

While the ability to combine data from various sources is a strength of the modeling approach, it also is a potential limitation. Although care was taken to choose studies with similar patient populations to the

MDS-003 trial and to control for known differences, a number of assumptions had to be made to estimate parameters when no definitive observational data were available. Most notably, we could not control for the potential impact of an interstitial deletion of the long arm of chromosome 5 on efficacy due to the small number of patients with deletion 5q abnormality in the “Nordic cohort.” With respect to clinical data on lenalidomide, the model relied heavily on the MDS-003 trial population as the source of information. Therefore, caution should be taken in generalizing the economic study results for the entire MDS patient population in the United States until further evidence on the representativeness of the MDS-003 study population characteristics is available. In addition, no precise MRU data was collected in any of the studies, and assumptions had to be made based on expert judgment on clinical treatment patterns in the United States. Utility estimates were obtained from interviews with MDS patients from a small study, although we note that there was relative consistency between ratings by patients from the United States, United Kingdom, and France from interviews with 30 additional patients in these countries. To address the limitations in the data, we performed sensitivity analyses that confirmed the robustness of the model results.

Researchers or decision-makers wishing to assess the potential to generalize the results to other health care settings should also take into account further possible cross-country differences or differences in the desired model framework. Practices related to BSC may well differ across countries, especially the use of EPO as part of the standard care for MDS patients. Specifically, while EPO is regarded as part of standard of care in the United States, it is used less frequently and for shorter periods of time in other health care systems. There is also some evidence on differences in unit costs across countries in MDS care that prohibits the direct transferability of cost-effectiveness results to other countries. In our analysis, a payer perspective was utilized, and for this reason no indirect costs, such as travel costs or caregiver time, were taken into account, which may be relevant to include in a study conducted from a societal perspective. The time horizon was the first year following the initiation of lenalidomide therapy. This time horizon was chosen given data availability from a phase II trial, the fast track designation status of lenalidomide, and the lack of data to inform longer-term extrapolation of the trial results. However, as recent follow-up data suggest that the duration of efficacy associated with lenalidomide is longer than 1 year, the time horizon of 1 year is short to capture the full impact of treatment. Furthermore, our model potentially underestimates some health care resource utilization, such as blood transfusion-related complications, and longer term transfusion-related health outcomes. Recent data suggest a signifi-

cant relationship between transfusion dependence and decreased survival.³ Thus, the cost effectiveness of transfusion independence reported here appears to be conservatively estimated and may be worth investigation in future research. Moreover, with the approval of oral iron chelators, the proportion of patients receiving chelation therapy would be expected to increase considerably compared to past experience utilizing parenteral chelators, with a corresponding disproportionate increase in costs in the comparator arm.

Conclusions

The results of this study suggest that in the United States, oral lenalidomide is a cost-effective treatment option for the management of transfusion-dependent anemia in patients with low- or intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality. The study also suggests that lenalidomide use results in reduced transfusion requirements and transfusion independence in trial MDS patients. A randomized, placebo-controlled phase III trial (MDS-004) is ongoing and will provide important data for validation of this model. This trial will not only provide more comparable data on efficacy of lenalidomide vs BSC, but also systematically collect MRU and health utility data from patients participating in the trial. Further investigation is therefore warranted to confirm these results as longer-term comparative data on efficacy, QOL, survival, and MRU become available from currently ongoing studies.

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