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Cost–effectiveness of treatments for high-risk myelodysplastic syndromes after failure of first-line hypomethylating agent therapy

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Purpose: To evaluate optimal salvage therapy in high-risk myelodysplastic syndromes patients who have failed a first-line hypomethylating agent (HMA) therapy, given that treatment choice is challenging. Methods: Using published literature and expert opinion, we developed a Markov model to evaluate the cost–effectiveness of current treatments for patients who failed first-line HMA therapy. The model predicted costs, life years, quality-adjusted life years and incremental cost-effectiveness ratios. Sensitivity analyses were conducted to assess the impact of uncertainty in model inputs. Results: Supportive care was the least expensive option ($65,704/patient) with the shortest survival (0.48 years). Low- and high-intensity chemotherapies and hematopoietic cell transplantation increased survival and costs with incremental cost-effectiveness ratios of $108,808, 306,103 and 318,163/life year, respectively. Switching HMA was more costly and less efficacious than another treatment option, namely low-intensity chemotherapy. Conclusions: Subsequent treatments in myelodysplastic syndrome patients who failed first-line HMA significantly increase costs, while only providing marginal clinical benefit and substantially increasing treatment-related morbidities. Additional treatment options would benefit resource allocation, clinical decision-making and patient outcomes.

KEYWORDS: cost–effectiveness analysis, economic modeling, health care resource utilization, hypomethylating agents, myelodysplastic syndromes

The myelodysplastic syndromes (MDS) comprise a group of hematopoietic malignancies characterized by cytopenias due to ineffective hematopoeisis, clonal cytogenetic and molecular abnormalities and a variable risk of progression to acute myeloid leukemia (AML) [1–3]. The incidence of MDS is estimated at between 5.3 and 13.1 per 100,000 in the general population and between 75 and 162 per 100,000 among those aged ≥ 65 years [4–8]. MDS prevalence in the USA is estimated to be 60,000–170,000 and is expected to increase [9,10].

Patients with high-risk MDS are typically treated first with hypomethylating agents (HMAs), that is, azacitidine or decitabine. These treatments were approved by the US FDA based on clinical studies showing disease remissions in 20% of patients, hematologic improvements in 40% of patients, transfusion independence in 50% of patients and prolonged survival in those receiving azacitidine [11–14]. However, such clinical improvements are transient, and the vast majority of MDS patients will lose response within 2 years [15].

Failing HMA therapy carries a grim prognosis for MDS patients; median survival is 17 months in low-risk MDS patients and <6 months in high-risk MDS patients [16–18].
There are three potential outcomes in MDS patients who failed HMA: one-third progress to AML, one-third have disease progression characterized by worsening cytopenias and their related complications and the last one-third discontinue therapies or succumb to complications [19]. Treatment choices after failing first-line HMA therapy in MDS include best supportive care (BSC), switching from one HMA to another, low-intensity chemotherapy (LIC; i.e., subcutaneous cytarabine), high-intensity chemotherapy (HIC; i.e., 7+3 induction chemotherapy in AML), allogeneic HCT and investigational clinical studies [17,18,20,21]. A recent comparison of these salvage treatments reported better outcomes with allogeneic HCT and investigational therapies compared with other treatments [16–18].

Given the limitations of current options and the unknown costs associated with these treatments, both providers and payers face challenges in deciding optimal treatments for these patients. In this study, we examined the clinical and financial outcomes of MDS patients who have failed first-line HMA treatment and constructed a health economic model to estimate the cost-effectiveness of available treatment strategies in the USA.

**Methods**

**Patient population & treatment**

We developed a US-based decision-analytic model that projected, from the payer perspective, the cost-effectiveness of currently available treatment options for high-risk MDS patients who progressed on or failed first-line HMA therapy. In this analysis, high risk is defined by the International Prognostic Scoring System (IPSS), revised IPSS (IPSS-R) score, and previous HMA failure [22,23]. HMA failure is defined as primary resistance to HMA or disease relapse. The published studies that formed the primary source for the study cohort used in this decision-analytic model also included IPSS low-risk MDS patients who were treated with HMA, although their numbers are very low. Hypothetical cohorts of patients were simulated to initiate one of the following treatments: BSC (red blood cell transfusions, platelet transfusions and growth factor support), LIC, HIC, switching HMA and allogeneic HCT. Clinical inputs were based on the published literature [3,16,18] and expert opinion, and costs were estimated from published literature [12, 24–31] and publicly available databases [32]. For each model strategy, we projected the costs (2014 US dollars) and life expectancy in life years (LYs) over a lifetime. These model outcomes were used to calculate incremental cost-effectiveness ratios (ICERs). The ICER is a metric describing the ratio of additional financial resources required for each 1 unit increase in clinical benefit when comparing two interventions. In this analysis, the ICER represents the additional cost in US dollars per 1-year gain in life expectancy.

**Model structure**

A Markov model, developed using TreeAge Pro 2012, was used to evaluate over a lifetime a hypothetical cohort of MDS patients who had progression or lost response while being treated with an HMA. A Markov model consists of mutually exclusive and exhaustive health states that reflect the condition of a patient at any given time. Patients resided in these health states and transitioned between them at the end of each model cycle, that is, each 4-week period. The model schematic is shown in Figure 1.

After entering the model at initiation of one of the second-line treatments (i.e., BSC, switch HMA, LIC, HIC, or HCT), patients could progress to acute myeloid leukemia (AML), experience a treatment- or disease-related adverse event
(thrombocytopenia, anemia and neutropenia-associated complications), discontinue treatment or die. Patients who progressed to AML accrued higher costs than those who do not; however, survival did not differ. Events were assumed to occur at the end of each 4-week cycle. During each cycle, costs, life expectancy, and clinical events were calculated. Due to the relatively short overall survival for patients with MDS, discounting was not applied. The lifetime costs and LYS were summed for each strategy to calculate model ICERs.

**Clinical inputs**

Clinical parameters for the model included those related to overall survival, treatment discontinuation and progression to AML (Table 1). Survival estimates were derived from published studies that evaluated second-line therapies in patients with MDS and from expert opinion [16,18]. Expert opinions were obtained through cognitive interviews with multiple clinical specialists (i.e., hematologists who regularly treat patients with MDS) from several academic institutions across USA. These cognitive interviews occurred after fully discussing the role of the model parameters and providing the clinicians with applicable literature for their review. Duration of treatment for patients switching HMA was estimated from the clinical trial used to inform HMA survival [18]. Due to limited published data, treatment duration estimates for the other model strategies (i.e., LIC, HIC), as well as the probability of progression to AML after initiation of second-line therapy, were estimated based on expert opinion after review of key published literature [16,18]. Specifically, patients were assumed treated with LIC for four 4-week cycles (i.e., 16 weeks) and with HIC for either two or three cycles (50% of patients with each). Following second-line treatment, patients progressed to BSC and remained on BSC for the remainder of their lives. Based on expert opinion, it was assumed that 35% of patients in any treatment would progress to AML.

**Cost inputs**

The following costs were included in the model: medication acquisition and administration, blood transfusions, HCT, BSC and AML management (Table 2). Costs were omitted from the analysis if they were equivalent for patients on all treatments, unrelated to the disease or treatments or uncommon and insignificant. Additionally, since the analysis was conducted from the payer’s perspective, indirect costs such as time and transportation costs and productivity losses were excluded. All costs were estimated from the payer’s perspective in the USA, and those reported prior to 2014 were inflated to 2014 $US using data from the Bureau of Labor Statistics [31].

Systemic therapy dosing data for switch HMA, LIC and HIC were described in an article outlining treatments for MDS patients [3]. Drug acquisition costs were based on wholesale acquisition cost (WAC) pricing [32], and HCT costs were estimated using results from an analysis of commercially insured HCT recipients [27]. Costs for BSC included physicians’ payments and supportive care medications, as well as transfusions due to disease-related adverse events. AML management costs, for the 35% of patients in the model who progressed from MDS to AML, incorporated costs of hospitalization, physician visits, supportive care medications and laboratory tests [21] and were estimated based on a study of Medicare beneficiaries diagnosed with AML residing in one of the Surveillance, Epidemiology, and End Results (SEER) registries [28].

**Adverse event inputs**

Patients could experience any of the following disease- and treatment-related adverse events at varying rates for each model strategy: thrombocytopenia, anemia and neutropenia. It was assumed that thrombocytopenia was treated with platelet transfusions, anemia was treated with red blood cell transfusions and an erythropoiesis-stimulating agent (ESA), and neutropenia was treated with a granulocyte colony-stimulating factor (G-CSF). The units of transfusions and growth factors required differed based on MDS. The requirements were estimated based on the published literature, claims analysis and expert opinion [33,34]. Red blood cell and platelet requirements range from 1.3 units per event for patients on BSC to 9.0 units for patients receiving HCT. Costs for platelet and red blood cell transfusions (Table 2) were derived from a cost-effectiveness analysis of first-line HMA therapy in patients with MDS [29]. It was

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**Table 1. Cost-effectiveness model inputs: clinical parameters.**

<table>
<thead>
<tr>
<th>MDS Treatment</th>
<th>Months</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSC</td>
<td>4.0</td>
<td>18</td>
</tr>
<tr>
<td>Switch HMA†</td>
<td>6.0</td>
<td>20, Expert opinion</td>
</tr>
<tr>
<td>LIC</td>
<td>7.3</td>
<td>18</td>
</tr>
<tr>
<td>HIC</td>
<td>8.9</td>
<td></td>
</tr>
<tr>
<td>HCT</td>
<td>19.0</td>
<td></td>
</tr>
<tr>
<td>Median treatment duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(number of 4-week cycles)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switch HMA‡</td>
<td>4.0</td>
<td>20</td>
</tr>
<tr>
<td>LIC</td>
<td>4.0</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>HIC</td>
<td>2.5</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>Proportion of patients</td>
<td>35%</td>
<td>22, Expert opinion</td>
</tr>
<tr>
<td>progressing to AML§</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This table shows the clinical inputs used in the model including: the overall survival for patients on each of the initial treatments; the number of treatment cycles patients receive; and the proportion of patients who progress to AML.

* Borthakur 2008 demonstrated 6-month median overall survival among patients treated with decitabine after azacitidine failure. Based on expert opinion, this estimate was assumed to be the same for patients treated with azacitidine after decitabine failure.

† Based on median time to progression.

‡ Patients are eligible to progress to AML while on any treatment, and at any point in the model. Patients who progress to AML accrue higher costs than those who do not, however survival does not differ.

assumed for costing purposes that patients can receive up to 2 units in a single infusion. Additionally, 40% of patients receive Filgrastim, and 50% receive Epoetin each model cycle regardless of treatment. Costs associated with hospitalization for these adverse events were not included in the model.

Utility inputs
The impact of MDS treatments and their associated adverse events on health-related quality of life were incorporated in model scenario analyses using utility weights (Table 2). Utility weights range between 0 and 1, with 0 representing death and 1 representing perfect health, and are multiplied by survival length to calculate model-predicted quality-adjusted life years (QALYs) associated with each model strategy. QALYs are a measure of efficacy that combine the length of survival with the quality of life during that period to better represent clinical benefits. A literature search for utility weights applicable to the patient population yielded no data for use in the model; therefore, expert opinion and a previously published survey of MDS patients were used to generate appropriate utility weight estimates for each strategy [35].

Analyses
In the base case, we evaluated the cost–effectiveness of second-line treatment options over a lifetime. ICERs were calculated as the ratios of incremental lifetime costs to LYS for each strategy. To assess the impact of parameter uncertainty on base case results, we conducted one-way and probabilistic sensitivity analyses. In one-way sensitivity analyses, all parameters varied individually at ±25% of base case values. In probabilistic sensitivity analyses, all parameters varied simultaneously for 1000 iterations. Cost parameters were varied based on gamma distributions and clinical parameters based on normal distributions with a mean of the base case value and a standard deviation of 10% of the base case.

In addition to sensitivity analyses, we conducted three scenario analyses to incorporate the impact of MDS and related treatments on quality of life:

Scenario 1: All MDS patients had the same health-related quality of life regardless of treatment and disease progression, and one utility weight was used for all patients (0.74);

Scenario 2: Quality of life differed for patients with MDS (utility weight = 0.74) and patients with AML (utility weight = 0.45);

Scenario 3: In addition to the changes in scenario 2 (differing quality of life between MDS and AML), we also assumed utility weights differed by treatment strategy.

We regenerated results for the three scenarios when incorporating these assumptions and reported the ICERS in terms of $/QALY. A probabilistic sensitivity analysis was also conducted for scenario 3, using the same distributions as previously mentioned for cost and clinical estimates and uniform distributions for utility weight estimates.

Results
Base case results
Among MDS patients who did not respond to or failed first-line HMA therapy, the model predicted that BSC was the least expensive option ($65,704 per person) and provided the shortest survival (0.48 years; Table 3). Patients switching HMA following first-line failure increased costs to $112,541 and extended survival modestly (0.24 years) compared with BSC. Patients treated with LIC and HIC had lifetime costs of
$108,791 and 169,702 and life expectancy of 0.88 and 1.08 years, respectively. Of all treatment strategies following first-line HMA failure, HCT patients survived the longest (2.26 years) and had the highest lifetime costs ($547,377).

Compared with BSC, the ICER for LIC was $108,808/LY gained, while HIC and HCT had ICERs of $306,103/LY and $318,163/LY, respectively (Table 3). The option of switching HMA was removed during ICER calculations due to strong dominance. Dominance is a concept in cost-effectiveness analyses, indicating that one treatment is superior in both costs and efficacy to another. In this case, LIC provides greater clinical benefit at a lower cost than switching HMA.

### Sensitivity analyses

In one-way sensitivity analyses, the strategies of switch HMA, HIC and HCT always had ICERs greater than $150,000/LY or were dominated for all parameter variations. The LIC ICER ranged from $87,000 to $120,000/LY and was most sensitive to survival inputs. There were no parameters with such an impact that any strategy would have an ICER below $87,000/LY.

Figure 2 depicts the cost-effectiveness acceptability curves. These curves show the probabilities of each strategy’s cost-effectiveness (along the Y axis) at different willingness-to-pay (WTP) thresholds (along the X axis). WTP represents the maximum financial outlay that one would find acceptable for a 1-unit gain in efficacy, creating a benchmark to allow decision makers to gauge whether an intervention provides a good value. The model predicted that BSC had a 99.5% probability of being the optimal strategy at a WTP threshold of $100,000/LY and was most likely to be the cost-effective strategy until the WTP was above $200,000/LY. At WTP thresholds above $200,000, LIC was the preferred strategy.

### Quality of life scenarios

In three separate scenario analyses, we assessed the impact on quality of life measures to calculate the ICER in terms of $/QALY. In scenario 1, when using one utility decrement to reflect lower quality of life for all MDS patients equally in the model, the ICERs were higher for every strategy. The estimated ICER for LIC was $145,489/QALY, compared with $108,808/LY in the base case, and ICERs for HIC and HCT increased to $410,280/QALY and $425,826/QALY, respectively. In scenario 2, when using the same decrement as in scenario 1 for patients with MDS and a second, lower utility for patients with AML, the ratios for LIC and HCT both increased to $149,768/QALY and $492,793/QALY, respectively. The strategies of switch HMA and LIC were both dominated. In scenario 3, when using different utility decrements for each strategy, the ICERs for LIC and HCT increased further to $194,490/QALY and $773,625/QALY, respectively. These results from scenario 3 were explored further in probabilistic sensitivity analyses, with the costs and QALY estimates for the nondominated strategies (i.e., BSC, LIC and HCT) shown in Figure 3.

### Discussion

To the best of our knowledge, this is the first economic evaluation of different treatment strategies that are currently in use for managing MDS patients who have failed first-line HMAs. On the basis of this cost-utility analysis using a Markov model that simulated the natural disease progression for an MDS patient’s...
lifetime, the ICER was lowest for LIC ($108,808/LY gained), followed by HIC ($306,103/LY gained) and HCT ($318,163/LY gained). An increase in life expectancy was seen with therapy intensification: best mean survival was estimated with HCT (2.26 years) and lowest with BSC (0.48 years). The unfavorable ICER observed with higher intensity treatment modalities can be biologically explained by the fact that while HIC or HCT offers the best possibility of rapid and relatively durable control of HMA-refractory disease compared with LIC or BSC, it comes with not only a higher treatment cost but also a price of higher rates of treatment-related complications resulting from profound myelosuppression, which oftentimes is followed by protracted count recovery or is due to graft-versus host disease in transplanted patients. This translates to increased utilization.

**Figure 2. Probabilistic sensitivity analyses results: cost-effectiveness acceptability curves.** These results are generated from the probabilistic sensitivity analyses, and show how many iterations out of 1,000 found a given strategy to be non-dominated and be the most efficacious strategy with an ICER below the given threshold.

**Figure 3. Probabilistic sensitivity analyses results: $/QALY scatterplot.** Depicted is the lifetime costs and QALYs for three non-dominated strategies in Scenario 3 across 1,000 iterations in which all input parameters were varied. QALY: Quality-adjusted life year.
of healthcare resources and consequently escalated costs of care. Organ dysfunction or toxicities from treatment intensification frequently have a negative impact on the quality of life (QoL), reflected in our model results in which $/QALY increased with more toxic treatment options such as HIC and HCT. The finding that our cost–effectiveness analysis did not identify a single best strategy resonates with the uncertainty that currently surrounds treatment decision making in these patients, due largely to the facts that only a very small proportion of patients meet transplant eligibility requirements following HMA failure and that the purported benefit, if any, of the prevailing MDS therapies after HMA failure have never been tested in randomized trials. By the same token, our model supports BSC as the preferred option for WTP threshold of up to $100,000/LY gained.

The cost of care for MDS is substantial and cumulative. While this study focuses exclusively on cost–effectiveness of interventions following first-line HMA failure, the upfront costs associated with disease treatment up to the time point when the disease is refractory to HMA can be considerable. In addition to the costs incurred with HMA use, these patients also receive other therapies before, concurrently with, or after HMAs and have high healthcare resource utilization costs. It is estimated that the annual costs in 2008 for azacitidine or decitabine alone was approximately $55,332 and $74,160, respectively [36]. To put this into perspective, among 18 of the most prevalent cancers in the USA, the 5-year cancer-related costs (after adjusting 2004 to 2014 dollars using the Consumer Price Index) was highest for MDS, exceeding $66,000 [37,38]. This raises the question of what threshold would be considered ‘socially acceptable’ cost-effective care for these patients. Although the $50,000 per QALY threshold for renal dialysis patients had been widely quoted in the USA as acceptable threshold, not only has this value become outdated but also there is no scientific justification for use of any one threshold as the sole determinant of economic efficiency [39]. In our analysis, we relied on cost–effectiveness acceptability curves rather than an arbitrary threshold to determine, which would be the most cost-effective treatment intervention across a range of WTP thresholds. As payers and providers place increasing importance on scientific evidence, survival and QoL benefits, treatment strategies must aim to make optimal use of available treatments while meeting the financial objectives of improving patient outcomes at reasonable cost.

This study is timely and important, as data extrapolated from several epidemiologic sources indicate that the segment of MDS patients who have failed first-line HMAs is increasing. An estimate of the growing burden of HMA-refractory MDS patients can be gleaned from the data collated from HMA-treated Medicare beneficiaries [37,40] and randomized trials [16–18]: >30,000 newly diagnosed cases of MDS each year [8]; a steady rise in HMA use with each calendar year since the introduction of azacitidine in 2004 (from 1.8% in 2004 to 11% by end of 2007) [37,40]; only 40–50% demonstrate clinical response to HMA with almost all losing response within 2 years [11,12,41,42] and increased clinical acceptance for using HMA in certain low-risk MDS cases in recent years. For patients who fail HMA, there is no standard of care or expert consensus treatment guidelines for second-line treatment. Current approaches to managing first-line HMA-refractory disease include enrollment in a clinical trial when feasible, allogeneic HCT with or without HIC, sequential switching to the alternative HMA or BSC – all approaches borrowed or modified from first-line setting. Additionally, some patients receive clofarabine as salvage therapy following HMA failure, although this option was not included in this analysis due to its rare use. Whether the MDS patients who are HMA nonresponders benefit from these approaches remains a controversial issue [43]. There might be a small benefit of sequential switching of HMA with one small retrospective analysis showing an overall response rate of 40% in decitabine-failed patients switched to azacitidine and 19% response rate in azacitidine-failed patients switched to decitabine [44]. Of note, in 40–67% of second-line patients switching HMA, the disease continued to progress with no improvement in survival. One study prospectively followed 14 azacitidine-failed patients who were switched to decitabine and reported a complete remission rate in only four patients [20]. Lenalidomide has been tried in various dosing regimens after HMA failure with a small benefit noted in those who harbored del5q abnormality [45]. Combinations of azacitidine with cytarabine [46], lenalidomide [47,48], anti-CD33 conjugate gemtuzumab ozogamicin [49,50] or histone deacetylase inhibitors [51] have shown promise when used in upfront treatment of high-risk MDS, but their role in HMA nonresponders remains undetermined. HIC is often attempted in HMA nonresponders, but limited data suggest poor outcome and less chance of remission. Allogeneic HCT, among all treatment modalities, is the only one to offer a possibility of cure in MDS patients whether in first line or in the refractory setting. With the introduction of HMAs in 2004, a large number of MDS patients have been treated with HMAs before proceeding to HCT [52]. Three retrospective analyses have, however, failed to show any improvement in overall survival regardless of whether the patients received azacitidine, HIC or azacitidine preceded or followed by HIC prior to transplant [53–55].

The biological rationale of applying first-line strategies in the second-line setting is questionable. Once the disease has progressed on a HMA, it is unlikely to respond to additional chemotherapy mainly because of clonal evolution that confers refractoriness to chemotherapy. Even at the time of MDS diagnosis, there is a high prevalence of comorbidities in the majority of the patients (e.g., 88% are >60 years, with 30–40% prevalence of comorbid conditions) [7] that precludes use of upfront HIC and HCT. Additionally, these patients acquire or develop newer comorbidities and organ toxicities over the course of the disease, rendering them highly vulnerable to toxicities of subsequent treatments once their disease has become refractory; this makes it even more difficult to proceed to therapies that were not considered feasible in the first-line setting. There is a clear unmet medical need for newer
treatments for this patient population, as current strategies are ineffective, limited by toxicities and not cost-effective.

In the absence of economic studies comparing cost–effectiveness of currently available MDS treatments following HMA failure, economic modeling provides a relevant framework within which MDS treatment costs and health gains can be compared. The strengths of this study are that the model reflects current treatment patterns in the USA, allows for combining data from various sources, uses efficacy data from published literature and calculates cost–effectiveness ratios based on standardized US cost estimates adjusted to current inflation trends. Because of a paucity of randomized or prospective data on these therapies, the majority of data were derived from small retrospective studies and a number of assumptions had to be made to estimate parameters based on expert clinical opinion. As this analysis was based on a payer perspective, no indirect costs, such as travel costs or caregiver time, were taken into account. This might be particularly relevant for MDS, which, although a rare disease, poses a disproportionately high economic burden from a societal perspective. This model was not designed to adjust for associated treatment costs such as blood transfusion-related complications and healthcare resource utilization related to hospitalization; as such, it may underestimate overall costs, which could be significant in those undergoing HCT with or without HIC. Additionally, the results are only generalizable to settings outside of the USA to the extent that costs are similar between countries.

Although lack of clinical benefit – more than cost – may be the primary reason that more aggressive treatment options are not always pursued in MDS, cost is also a consideration. This is particularly apparent when considering the ever-increasing healthcare expenditures in the USA and evaluating the increasing focus on value-based care by leading cancer societies, most notably American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH). The results of this study highlight the limited utility of current approaches in HMA-failed MDS patients from a cost–effectiveness perspective and underline the need for novel therapies that are affordable, have a favorable risk–benefit profile with tolerable toxicities and preserve QoL to thereby be more acceptable to payers, providers and patients alike.

Financial & competing interests disclosure
Onconova Therapeutics, Inc. funded the research described in the manuscript. TJ McKearn and ME Petrone are employees of Onconova Therapeutics, Inc. and at the time the analyses were conducted S Megaffin was also an employee — he is now President of Churchill Pharmaceuticals. TGK Bentley, JD Ortendahl and AM Anene are employees of Partnership for Health Analytic Research, LLC, which received payment from Onconova Therapeutics, Inc. to conduct the analyses described in this manuscript. CR Cogle and S Mukherjee have consulted with Partnership for Health Analytic Research, LLC. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Peer reviewers on this manuscript were reimbursed for their time.

Key issues

- Myelodysplastic syndromes (MDS) are hematopoietic malignancies that most commonly occur in elderly patients and appear to be increasing in prevalence in the USA.
- High-risk MDS patients are typically treated first with hypomethylating agents (HMAs; i.e., azacitidine or decitabine). Clinical improvements are seen in only half of patients, and the vast majority of patients eventually lose response.
- We developed a new cost–effectiveness model to assess treatment options for MDS patients failing first-line HMA therapy.
- The model predicted that the least to most costly strategies were: best supportive care, switching HMA, low-intensity chemotherapy, high-intensity chemotherapy and hematopoietic cell transplantation.
- High-intensity chemotherapy and hematopoietic cell transplantation had the highest expected survival, but also the highest rates of treatment and disease-related adverse events.
- Switching HMA was dominated (higher costs, lower survival than another option), and best supportive care was the most attractive strategy within the willingness-to-pay threshold of ≤$100,000/life year.
- The results of this study highlight the limited utility of current approaches in HMA-failed MDS patients from a cost–effectiveness perspective and underline the need for novel therapies that are affordable, have a favorable risk–benefit profile with tolerable toxicities and preserve quality of life.
References
Papers of special note have been highlighted as:
• of interest
•• of considerable interest
• This is the first study to report on the high number of uncaptured MDS cases in the SEER registries and proposes a novel algorithm to maximize MDS case abstraction for more accurate incidence estimation.
•• This is the seminal study to show the dismal outcome of MDS patients once they fail hypomethylating therapy and the challenges faced in managing these patients.