Impact of timing of achievement of red blood cell-transfusion independence on clinical outcomes and resource utilization in lower-risk myelodysplastic syndromes

MDS-008

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Introduction

- Myelodysplastic syndromes (MDS) are a group of malignancies characterized by ineffective erythropoiesis leading to different types of cytopenia (eg, anemia) and can progress to acute myeloid leukemia (AML)[1,2]
- Patients often require red blood cell (RBC) transfusions for treatment of anemia
- RBC-transfusion dependence (RBC-TD) is associated with decreased overall survival (OS) and quality of life, and increased morbidity[2-4]
- In lower-risk MDS (LR-MDS), treatment goals include reducing transfusion burden (TB), alleviating disease symptoms, improving health-related quality of life, and preventing or delaying progression to higher-risk MDS (HR-MDS) and AML, which are associated with lower survival[2,3,5]
- Erythropoiesis-stimulating agents are the most common treatments to manage anemia for patients with LR-MDS during first-line (1L) treatment
- Luspatercept is being investigated for 1L treatment of anemia in the phase 3 COMMANDS trial (NCT03682536)[6-8]
- Second-line (2L) treatment includes luspatercept (the MEDALIST trial; NCT02631070) and, if approved, azacitidine[2,9,10]
- The impact of achieving a clinical benefit during 1L versus 2L treatment for patients with LR-MDS as well as long-term outcomes and healthcare resource utilization (HCRU) remains uncertain

Objective

- To estimate the clinical outcomes, complications, and HCRU associated with achievement of RBC-transfusion independence (RBC-TI) during 1L versus 2L treatment among patients with TD LR-MDS

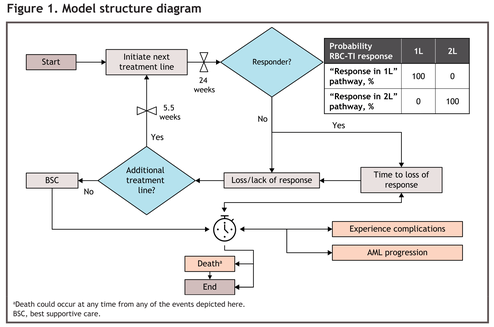
Methods

- To answer the decision problem, a disease burden model was developed to simulate the disease course for patients with LR-MDS starting from 1L treatment initiation until death (a lifetime analysis)

Model approach

- A discrete-event, individual patient simulation model tracks outcomes for 2 hypothetical disease pathways and compares the 2 pathways (**Figure 1**)
  - Individual patients were randomly sampled from patient profiles[6]
  - The disease course of each sampled profile was then simulated once on the first hypothetical pathway, and then again on the second pathway
  - A total of 9980 simulations were conducted for each analysis
  - The 2 hypothetical pathways were defined based on the occurrence of response during 1L treatment and then 2L treatment: "Response in 1L" and "Response in 2L"
- Response was defined as RBC-TI for ≥ 12 weeks within the first 24 weeks since treatment initiation, aligned with a key secondary outcome from the COMMANDS trial[6]
- The model included functionality for parameters to vary by low TB (LTB) and high TB (HTB), the cutoff of which could be changed; HTB was defined as ≥ 4 units/8 weeks in the base case
- The model reported in the related abstract contains data from the interim analysis of the COMMANDS trial; this model was updated with data from the latest COMMANDS data cut (March 31, 2023)

Figure 1. Model structure diagram



[a]Death could occur at any time from any of the events depicted here.
BSC, best supportive care.

Response, loss of response, and non-response

- After achievement of response from either 1L or 2L treatment, time to loss of response was modeled by random sampling from duration of response curves
  - For 1L, parametric curves were fit to patient-level data (PLD) from COMMANDS[6]
  - For 2L, curves were fit to MEDALIST PLD[10]
  - Curve selection was determined based on fit statistics and clinical plausibility
- Patients who did not respond or stopped responding to 1L treatment then initiated 2L treatment after an additional 5.5 weeks (median time between treatment lines in COMMANDS)[6]
- Patients who did not respond to 2L treatment or stopped responding to 2L treatment then initiated BSC and were assumed to be RBC-TD for the remainder of their lifetime

OS

- Patients who initiated each line in the disease pathway were subject to a probability of death during the response assessment window (24 weeks) and thereafter, time to death is sampled from curve fits to OS data
  - For 1L, parametric extrapolations were fit to COMMANDS OS PLD, stratified by response status[6]
  - For 2L treatment, a parametric fit for patients who are TI was derived from published Kaplan-Meier data[11]
    - For TD patients, a hazard ratio (HR) of 2.732 was applied to this TI reference[4]
- In addition to disease-specific OS, to ensure the estimated parametric survival fits did not result in better survival than the general population, patients were also subject to general population mortality based on 2020 US life table data[12]

AML

- Throughout the time horizon, time to AML was sampled using parametric fits to published data for TI patients,[11] to which an HR for TD patients was applied
  - The HR for TD[13] versus TI patients was 1.76
- Upon onset of AML, time to death was simulated using 2 parametric fits to published Kaplan-Meier curves for:
  - Active treatment
  - BSC (fits were weighted in the model assuming 82% received active treatment)[14,15]

Clinical complications, HCRU, and utility values

- Annual rates of clinical complications, HCRU, and utility values were stratified by TI/TD with AML rates assumed the same as TD (**Table 1**)
- Quality-adjusted survival was calculated by applying health utility values (ranging from 0 to 1, where 1 is perfect health) to survival
  - Utility values were stratified by TB and by those with AML (**Table 1**)

Table 1. Annual rates of clinical complications,[a] HCRU, and utility values[b] given health status

Health status	Cardiac events[16]	Infection[16]	Bleeding[16]	Hospitalization[16]	ED visits[16]	Utility value
TI	0.01	0.61	0.23	0.37	0.51	0.85[17]
LTB	0.076	1.57	0.64	1.91	1.59	0.77[17]
HTB						0.65[18]
AML						

[a]TI uses TI rate reported,[16] LTB/HTB uses TD rate reported,[16] and AML assumed equal to TD; [b]TI uses TI utility reported,[17] LTB uses average of TI and TD utility reported,[17] HTB uses TD utility reported,[17] and AML utility for induction phase assumed.[18] ED, emergency department.

Analysis

- Model outcomes (life years [LYs], quality-adjusted life years [QALYs; where 1 QALY = 1 year in perfect health], lifetime RBC units) were averaged across all simulations for each disease pathway
- Patient-level model outputs of TB status, AML status, and survival over time were analyzed and averaged across all simulations (**Figure 2**)
- Scenario analyses were conducted to assess the impact of model parameters, settings, and assumptions
  - Select key scenarios included: limiting the response time during 1L treatment, assuming an improved survival for LTB compared with HTB (HR of 1.866 vs 2.732), sourcing 1L OS from the literature rather than COMMANDS (same source as 2L),[4,11] analyzing subpopulations (lower TB at baseline, < 70 years of age), and varying utility inputs (TI: 0.76; TD: 0.69)[19]
- For those patients that responded during 2L treatment, time to loss of response was capped at a maximum response time of 95.7 months (per feedback from a clinical expert)
- Time to loss of response during 1L treatment was capped at 191.4 months, which was assumed to be twice that of 2L based on visual inspection of the trial data that showed improved duration of response in 1L versus 2L

Results

Base case results

- Patients in the "Response in 1L" pathway spent more time TI versus TD and experienced longer quality-adjusted survival than those in the "Response in 2L" pathway (**Table 2**)
- Patients in the "Response in 1L" pathway versus "Response in 2L" experienced fewer clinical complications and required fewer RBC units, suggesting a lower patient and economic burden
- Due to mortality prior to initiating 2L (ie, mortality during the 24-weeks assessment time in 1L and during the time delay between 1L and 2L), delaying response until 2L led to fewer patients responding overall in 2L (see relative height of the TI peaks in the health status tracking [**Figure 2**])

Scenario analyses

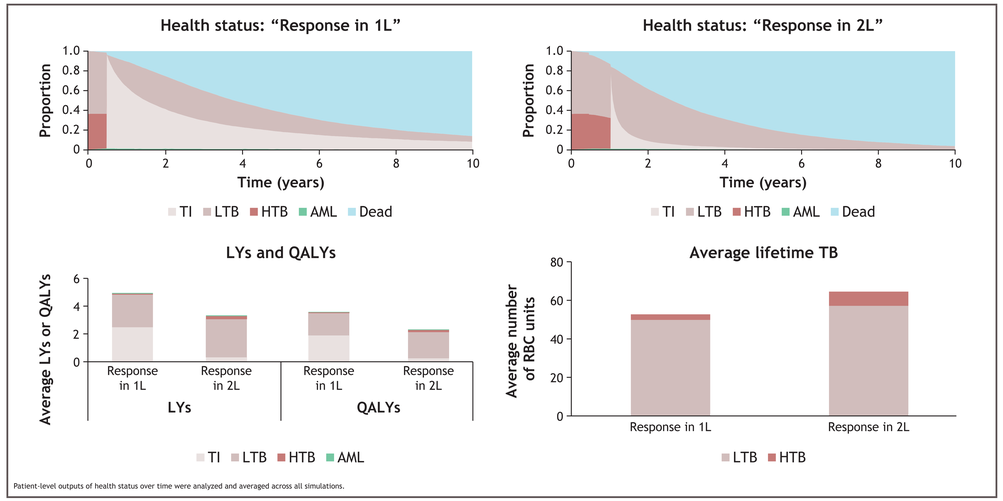
- Quality-adjusted survival and lifetime RBC units for the base case and scenarios (both pathways and the difference between them) are shown in **Figure 3**

Table 2. Summary of results

Outcome, mean[a]	"Response in 1L" pathway	"Response in 2L" pathway	Incremental outcome
Survival, months	59.4	40.0	19.4
Quality-adjusted survival, months	43.1	27.9	15.2
Lifetime RBC units	52.65	64.46	−11.81
RBC units/16 weeks	3.26	5.93	−2.67
Infections[b]	1.10	1.54	−0.45
Bleeding events[b]	0.44	0.63	−0.19
Hospitalizations[b]	1.15	1.84	−0.69
ED visits[b]	1.06	1.55	−0.49

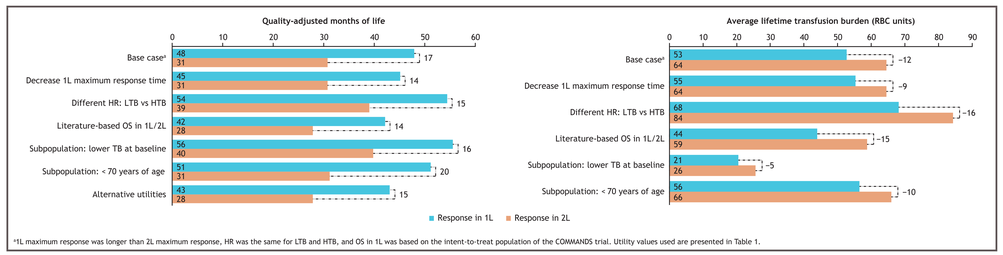
Results reflect a lifetime analysis, ie, from 1L initiation until death.
[a]Numbers may not add up due to rounding; [b]Values are reported as annual rates per patient.

Figure 2. Health status tracking, LYs and QALYs, and TB



Patient-level outputs of health status over time were analyzed and averaged across all simulations.

Figure 3. Scenario analyses for quality-adjusted survival and TB



*1L maximum response was longer than 2L maximum response, HR was the same for LTB and HTB, and OS in 1L was based on the intent-to-treat population of the COMMANDS trial. Utility values used are presented in Table 1.

- In all scenarios, "Response in 1L" showed greater quality-adjusted survival than "Response in 2L" (17-month increase in the base case; range, 14-20 months in scenarios)
  - The quality-adjusted survival benefit of achieving response in 1L was slightly decreased if response time in 1L was limited, if the survival differential was smaller for TI versus TD, and if alternative utility values were used with less difference between TI versus TD[19]
  - In a younger population, the quality-adjusted survival benefit of "Response in 1L" was even greater than in the base case
- "Response in 1L" consistently led to lower transfusion burden than "Response in 2L", although the difference in lifetime RBC units between the 2 pathways was modest in some scenarios (**Figure 3**)
  - There was an interplay between survival and TB in that patients with improved survival also accumulate more lifetime RBC units

Limitations

- Alternative data sources were considered for parameterizing the model (eg, OS); however, due to misalignment of the population and/or outcomes, these were not pursued
- Other than progression to AML, no additional disease progression was modeled, such as increase in TB over time or progression to HR-MDS, due to limited or lack of data, suggesting these are important clinical components of the disease course
- This analysis extrapolated survival data beyond the follow-up time available from the COMMANDS and MEDALIST trials, which introduced uncertainty into the model, potentially influencing the results
- The patient populations evaluated are from randomized controlled trials; therefore, results may not be generalizable to patients treated in clinical practice

Conclusions

- Based on our model analyses, for patients with TD LR-MDS, experiencing an RBC-TI response during 1L treatment rather than 2L treatment led to a lower lifetime TB, resulting in greater survival benefit, improved quality-adjusted survival of 17 months, fewer transfusions, and reduced HCRU
- Initiating treatments that enable RBC-TI during 1L treatment rather than delaying efficacious therapies until 2L treatment may be more optimal management of anemia in the treatment of LR-MDS

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