The patient voice: measuring what matters in lower-risk myelodysplastic syndromes treated with imetelstat

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IMerge, a phase III randomized, double-blind, placebo-controlled study investigated imetelstat in patients with transfusion-dependent relapsed/refractory lower-risk myelodysplastic syndromes (LR-MDS) after erythropoietin therapy or in those who were ineligible for erythropoietin. Imetelstat not only resulted in significantly higher ≥8-week red blood cell (RBC) transfusion independence rates compared with placebo (40% *vs*. 15%, *P*=0.0008), but also demonstrated durable responses, with a median duration of transfusion independence of approximately one year, a truly meaningful interval for the patient. Although grade 3-4 treatment-emergent adverse events (most commonly neutropenia and thrombocytopenia) occurred in 91% of patients, they remained transient, and no treatment-related deaths were reported.[1] These temporary cytopenias were also associated with response to imetelstat.[2]

Because LR-MDS is associated with improved survival outcomes and lower risk of transformation to acute myeloid leukemia compared with higher-risk disease, treatment has historically focused on symptom management. Fatigue, one of the most common and debilitating symptoms reported by patients, has been associated with anemia in LR-MDS. While RBC transfusions may provide temporary relief, transfusion dependence imposes substantial logistical and psychological burdens. With global shortages in blood products, continued transfusions inflict both patient and societal burdens. Long-term complications from iron overload and frequent clinic and hospital visits associated with RBC transfusion dependence further erode patients' Quality of Life (QOL) over time. Therefore, patient-reported outcomes (PRO) have been increasingly emphasized as essential endpoints in clinical trials for LR-MDS. The clinical relevance of PRO has been previously demonstrated, with patient-reported fatigue identified as an independent prognostic factor for overall survival, comparable to risk stratification by established prognostic scoring systems.[3]

Over the past decade, clinical trials in LR-MDS have transitioned from survival-based clinical outcomes to surrogate hematologic endpoints, such as hematologic improvement and transfusion independence, with the reasonable hypothesis that these outcomes translate into meaningful clinical benefit for the human suffering from MDS. However, multiple observational studies have shown that hemoglobin levels and QOL measurements are not always consistently correlated.[4] Table 1 summarizes pivotal phase III trials in LR-MDS, including their primary endpoints and QOL assessments, highlighting the fact that robust improvements in QOL have not been observed despite clear hematologic benefit. These findings raise the critical question: do hematologic responses truly make patients feel better (enough)?

MEDALIST, a phase III randomized, double-blind, placebo-controlled clinical trial studying luspatercept in transfusion-dependent relapsed/refractory LR-MDS after erythropoietin, demonstrated higher ≥8-week RBC transfusion independence rates with luspatercept compared with placebo (38% *vs*. 13%, *P*<0.001).[5] However, no clinically meaningful differences in QOL were observed between treatment groups or by response status.[6] In contrast, in this issue, Sekeres *et al*. report QOL outcomes from IMerge in a nearly identical relapsed/refractory LR-MDS patient population to that of MEDALIST.[7] By using 3 validated instruments (Functional Assessment of Chronic Illness Therapy – Fatigue [FACIT-F], Quality of Life in Myelodysplasia Scale [QUALMS], and Functional Assessment of Cancer Therapy – Anemia [FACT-An]), imetelstat was associated with patients reporting sustained improvements in QOL compared to placebo. Among patients receiving imetelstat, those who achieved transfusion independence experienced significantly greater QOL improvement than non-responders at eight weeks (70% *vs*. 37%, *P*<0.001), 24 weeks (73% *vs*. 41%, *P*=0.004), and one year (88% *vs*. 44%, *P*=0.002). These data are particularly invaluable in the field of LR-MDS, where hematologic improvement has

not consistently translated into patient-perceived clinical benefit.

Several aspects of the QOL data from this article merit emphasis. First, the use of multiple PRO instruments was a truly comprehensive physical, emotional, and functional assessment, demonstrating that observed clinical benefit extends beyond fatigue alone. Figure 1 illustrates downstream symptoms in LR-MDS and tools used to measure their impact. Though regulatory approval has been traditionally based on hemoglobin improvement and decreased RBC transfusion frequency, the field is evolving toward using PRO when assessing the true benefit of a drug. Second, the improvement in QOL in 8-week, 24-week, and 1-year responders who have achieved transfusion independence indicates a clear association between RBC transfusion independence and recognized (by the patient) clinical benefit. Lastly, the sustained PRO improvements over multiple cycles of imetelstat is particularly noteworthy. In the setting of therapy intended to be administered long term with a dosage of every four weeks and at least monthly follow-up visits for these infusions, the lack of any deterioration in QOL with subsequent cycles is quite reassuring. The durable PRO improvements also suggest that the high rates of treatment-related neutropenia and thrombocytopenia in early cycles did not translate into clinical manifestations. Nonetheless, the interpretation of QOL data in LR-MDS trials remains challenging. As patients receiving imetelstat and placebo undergo RBC transfusions to maintain hemoglobin at or near acceptable levels, observable differences in PRO may be blunted, thus lacking the sensitivity needed to detect incremental clinical benefit attributable solely to investigational therapy.

In conclusion, IMerge demonstrates that imetelstat improves not only RBC transfusion independence rates, but also QOL across multiple domains. In all of medicine, especially in LR-MDS (a chronic disease with a median survival

Table 1. Phase III studies in lower-risk myelodysplastic syndromes with quality-of-life measurements.

Study	Treatment	Primary endpoint	Results	QOL measurements	QOL findings
ECOG E1996[9]	EPO±G-CSF *vs.* supportive care	Erythroid response at 4 months	36% (EPO) *vs.* 10% (supportive care)	FACT-G, FACT-F	No significant difference between groups, responders with improvement
Platzbecker *et al.* (2017)[10]	Darbepoeitin *vs.* placebo	Transfusion incidence from weeks 5-24	36% (darbepoeitin) *vs.* 59% (placebo)	FACIT-F, EQ-VAS	No significant difference between groups or by response
Fenaux *et al.* (2018)[16]	EPO *vs.* placebo	Erythroid response through week 24	32% (EPO) *vs.* 4% (placebo)	FACT-An, EQ-5D	No significant difference between groups, responders with improvement
MDS-004[11]	Lenalidomide 10 mg *vs.* 5 mg *vs.* placebo	Transfusion independence ≥26 weeks	55% (lenalidomide 10 mg) *vs.* 35% (lenalidomide 5 mg) *vs.* 6% (placebo)	FACT-An	Significant improvement in lenalidomide arms and responders
MDS-005[12,13]	Lenalidomide *vs.* placebo	Transfusion independence ≥8 weeks	27% (lenalidomide) *vs.* 3% (placebo)	EORTC QLQ-C30	Significant improvement in lenalidomide arm and responders
MEDALIST[5,6]	Luspatercept *vs.* placebo	Transfusion independence ≥8 weeks	38% (lusptarecept) *vs.* 13% (placebo)	EORTC QLQ-C30, QOL-E	No significant difference between groups or by response
COMMANDS[14,15]	Luspatercept *vs.* EPO	Transfusion independence ≥12 weeks with Hb increase ≥1.5 g/dL at 24 weeks	59% (luspatercept) *vs.* 31% (EPO)	EORTC QLQ-C30, QOL-E	Shortened time to QOL improvement with luspatercept

ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EPO: erythropoietin; EQ-5D: 5-Item European Quality of Life Five Dimensions; EQ-VAS: European Quality of Life Visual Analog Scale; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-An: Functional Assessment of Cancer Therapy – Anemia; FACT-F: Functional Assessment of Cancer Therapy – Fatigue; FACT-G: Functional Assessment of Cancer Therapy – General; G-CSF: granulocyte colony stimulating factor; Hb: hemoglobin; QOL: Quality of Life; QOL-E: Quality of Life E.

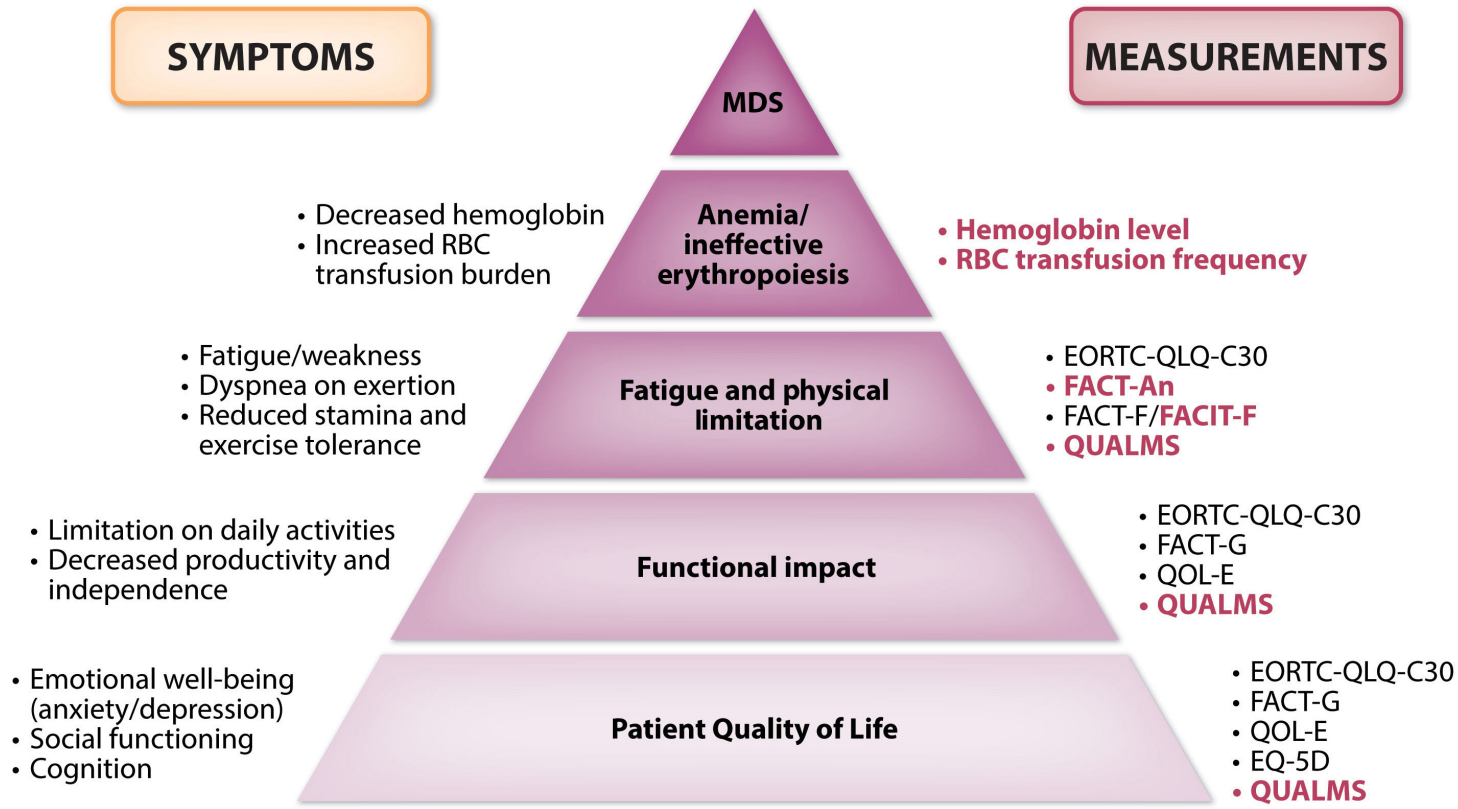

Figure 1. Model with downstream effects experienced by patients with lower-risk myelodysplastic syndromes and tools for measurement. Downstream symptoms in lower-risk myelodysplastic syndromes (MDS) and tools used to measure their impact, with those employed in IMerge highlighted in red. EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D: 5-Item European Quality of Life Five Dimensions; EQ-VAS: European Quality of Life Visual Analog Scale; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-An: Functional Assessment of Cancer Therapy – Anemia; FACT-F: Functional Assessment of Cancer Therapy – Fatigue; FACT-G: Functional Assessment of Cancer Therapy – General; RBC: red blood cell.

of approximately 5-11 years; interquartile range 2-17),[8] we certainly discuss survival with patients but also always emphasize QOL. In LR-MDS, where alleviating symptom burden and improving daily function in patients are as (and sometimes more) important than extending length of life, this study sets an important precedent: effective therapy should also be judged by its impact on patients' daily lives, not solely by laboratory values or transfusion metrics. IMerge is one of the first truly meaningful demonstrations of improved QOL with MDS therapy.

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Contributions

Both authors wrote and reviewed the manuscript, and approved the final version for publication.

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