Clinical Approach to Relapsed or Refractory Lower-Risk Myelodysplastic Syndromes

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Lower-risk myelodysplastic syndromes (LR-MDS) although are considered an indolent disease, yet population-level outcomes demonstrate a substantial survival decrease compared with age-matched controls. In large international datasets of untreated primary MDS, median overall survival (mOS) varies by IPSS-R category, but remains clinically meaningful even in lower-risk strata (e.g., very low: 8.8 years; low: 5.3 years; intermediate: 3.0 years), and LR-MDS patients experience an estimated mean life-year loss of 6.3 years versus the general population. These observations indicate the need for a management strategy that goes beyond supportive care only, aiming to improve both quality of life and survival while minimizing treatment toxicity—particularly in an elderly, comorbidity-burdened population.Anemia and transfusion dependence represent the dominant clinical problem in LR-MDS and a key driver of outcomes. Serial landmark analyses show that red blood cell transfusion dependence (RBC-TD) is associated with markedly worse mOS compared with transfusion independence (RBC-TI) (e.g., 45 vs 98 months), and the adverse impact of anemia is biologically and clinically plausible: higher cardiovascular morbidity/mortality, transfusional iron overload, and increased leukemic evolution risk are all highlighted as contributors. Transfusion itself, although saving life, is not devoid of side effects: one unit of blood contains ~200–250 mg of iron, and cumulative exposure (e.g., 20 units ≈ 4 g iron) rapidly leads to iron overload and organ damage. First-line anemia therapy historically relied on erythropoiesis-stimulating agents (ESAs), and early ESA initiation is associated with better responses and longer duration of benefit (responses and response duration appear superior when therapy begins within 6 months of diagnosis). Achievement of transfusion independence and increase of hemoglobin upon ESA therapy is associated with prolonged survival. Many LR MDS patients, however, lose response to ESAs or do not respond, becoming transfusion dependent.Therefore, a clinical approach to relapsed/refractory (R/R) LR-MDS should be anchored in (i) early identification of patients at risk for escalation in transfusion burden (TB), (ii) timely initiation of effective erythroid-directed therapy, selecting patients with lower IPSS-R and IPSS-M, serum EPO levels < 200U/L (or at least < 500U/L) and transfusion independent (iii) structured sequencing of available disease-directed options once ESA benefit is lost or unlikely. In the R/R setting—patients who fail, relapse after, or are intolerant to ESA (or are ESA-ineligible due to high endogenous EPO)—sequencing should be individualized by disease features (TB, Hb level, sEPO, RS/*SF3B1*) and prior exposures. Cytogenetic and molecular stratification remains essential in R/R LR-MDS to match mechanism to biology. For TD del(5q) LR-MDS, lenalidomide remains an extremely effective agent in inducing transfusion independence and increase of hemoglobin. Early low-dose lenalidomide in anemic non-transfusion-dependent disease it was recently shown to prolong time to transfusion dependence and achieved high HI-E and cytogenetic response rates (time to TD ~66.3 vs 11.6 months; HI-E 70% vs 0%; cytogenetic response 80% vs 0%). Luspatercept is a recombinant fusion protein comprising a modified extracellular domain of the human activin receptor type IIB (ActRIIB) fused with the Fc domain of human IgG1. It enhances terminal erythroid maturation by trapping activin receptor type IIB ligands, reducing SMAD2/3 signaling, inducing transfusion independence (TI) in ESA-relapsed/refractory (R/R) TD LR-MDS patients especially, but not only, with ring sideroblasts (MDS RS). Luspatercept is approved for TD LR MDS patients of all subtypes, having shown activity in real life studies, after the efficacy was demonstrated in the MEDALIST investigation for MDS RS/*SF3B1*mut, a double-blind, placebo-controlled phase 3 trial in which patients who had been receiving regular red blood cell transfusions and were refractory to ESAs, were randomized to receive luspatercept or placebo. Of the 222 patients enrolled, 202 (91%) carried a somatic mutation in *SF3B1*. Overall, 38% of patients in the luspatercept group achieved transfusion independence for more than 8 weeks compared with 13% in the placebo group. But when the entire treatment period was considered, 47.7% of patients achieved transfusion independence, accompanied by prolonged overall survival. Luspatercept was used at the escalating doses of 1.0- 1.75 mg/kg every 3 weeks sc. The safety signal was good. Neutrophil and platelet recovery, in parallel with Hb increase, was also observed. For the patients who achieved transfusion independence (TI) >8 weeks, 41.3% of cases had an interrupeted period of TI > 1year. Overall, median duration of TI was 79.9 weeks vs 21 weeks for placebo.An active strategy could be improved by using luspatercept at the maximum approved dose upfront in transfusion-dependent LR-MDS (as it is suggested in the ongoing clinical trial MAXILUS phase 3b): patients were assigned to ESA-naïve versus ESA-R/R/I cohorts, treated with luspatercept 1.75 mg/kg Q3W, with primary efficacy defined as RBC-TI ≥8 weeks plus Hb increase ≥1 g/dL (weeks 1–24). Preliminary efficacy signals are reported in both cohorts, including meaningful Hb increases and RBC-TI endpoints in ESA-R/R/I patients, alongside a manageable safety profile (with TEAE summaries provided). For patients with persistent transfusion dependence after ESA and/or luspatercept, imetelstat represents a disease-modifying option supported by randomized phase 3 evidence in TD LR-MDS. In IMerge phase 3 (IPSS low/intermediate-1; R/R to ESA or ESA-ineligible with EPO >500 mU/mL; TD ≥4 RBC units/8 weeks; non-del(5q); no prior lenalidomide or HMAs), imetelstat 7.5 mg/kg IV every 4 weeks significantly increased RBC-TI rates versus placebo: ≥8-week TI 40% vs 15%, ≥24-week TI 28% vs 3%, and ≥1-year TI 18% vs 2% . Among responders, TI was durable with sustained responses over time and exploratory analyses show low rates of AML progression with median PFS not reached in either arm; AML progression was uncommon (e.g., 1.7% vs 3.3%). Safety is characterized predominantly by hematologic toxicity—grade 3–4 thrombocytopenia and neutropenia were frequent (especially early cycles), with non-hematologic AEs generally low grade. Pooled analyses of imetelstat treated patients suggest clinical activity regardless of prior treatment exposures (ESAs, luspatercept, lenalidomide), while indicating more modest activity in heavily pretreated subsets (e.g., prior HMA). Disease modifying activity of imetelstat has been suggested by the significant decrease in variant allele frequency of somatic mutations correlating with hematological response.Targeted therapy opportunities, though applicable to smaller subsets, are also represented: *IDH*mut inhibitors have shown signals even in LR-MDS after EPO failure (e.g., in an *IDH2*-mutated LR-MDS cohort, 55% patients achieved complete remission with transfusion independence and no toxicity in the reported experience). In the phase 3 COMMANDS trial (ESA-naïve TD LR-MDS; IPSS-R very low/low/intermediate; sEPO <500 U/L; <5% blasts; del(5q) excluded), luspatercept significantly improved the primary endpoint (RBC-TI for ≥12 weeks with concurrent mean hemoglobin [Hb] increase ≥1.5 g/dL during weeks 1–24) versus epoetin alfa (60.4% vs 34.8%; p<0.0001). Benefits extended across clinically relevant subgroups (baseline TB strata, sEPO categories, *SF3B1* mutation status, and ring sideroblast [RS] status), and durability signals were compelling: RBC-TI ≥12 weeks (week 1–EOT) occurred in 76.4% vs 55.8%, with longer cumulative response duration (median cumulative duration ~150.0 vs 95.1 weeks) and a consistent safety profile over >2.5 years. In summary, a contemporary clinical approach to R/R LR-MDS should treat anemia as a disease-defining, outcome-linked manifestation rather than a purely symptomatic issue. The data support proactive therapy to achieve durable RBC-TI (ideally with meaningful Hb recovery), reduce transfusion-related complications (including iron overload), and potentially improve survival. Evidence-based sequencing begins with early ESA use when appropriate, transitions to luspatercept when response is lost, but consider this agent not only in R/R cases, but also as an effective and durable first-line option (with subgroup-consistent benefit), for TD ESA-naïve LR-MDS who do not have probability to respond to ESAs and incorporates imetelstat as a potentially disease-modifying therapy in ESA-failed/ESA-ineligible and luspatercept-failed TD LR-MDS, especially if with high transfusion burden. Molecularly targeted agents and cytogenetically defined approaches (e.g., lenalidomide in del(5q), ivosidenib and enasidenib in *IDH1*/*IDH2* mutated cases) further refine care for select patients, providing a structured pathway for R/R disease that is both biologically informed and clinically meaningful.