

Letter

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Real-world Data From the Swiss Lenalidomide in MDS del(5q) (SLIM)—Registry Identify New Chances and Challenges in Lenalidomide Treatment of Patients With MDS del(5q)

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Myelodysplastic syndromes (MDS) constitute a heterogeneous group of clonal hematopoietic disorders characterized by ineffective hematopoiesis, persistent peripheral blood cytopenias, and an increased risk of transformation to acute myeloid leukemia (AML).¹ Treatment with lenalidomide has been recommended for patients with MDS and 5q deletion with symptomatic anemia and a high-transfusion burden with red blood cells (RBC) by several guidelines.^{2–4} Little is known about usage, chances, and challenges in daily clinical practice to comply with these guidelines. To close this informative gap an observational, multicenter, national registry, involving the whole spectrum of hematologists and oncologists from primary to tertiary health care centers in Switzerland—the Swiss Lenalidomide in MDS del(5q)-Registry (SLIM-Registry)—was established.

The SLIM-Registry is a web-based clinical data management application. Data entry was performed retrospectively, after at least one cycle of lenalidomide has been applied, and locally by each participating center via a password-protected log-in at the website (www.slim-registry.ch). Eligible patients were 18 years

of age or older and had a MDS and a del(5q) with or without additional cytogenetic abnormalities. Patients were either treated with lenalidomide in the past or treatment with lenalidomide was ongoing at entry into the registry. All living patients provided written informed consent. Patients with MDS without a confirmation of del(5q) were not eligible. The SLIM-Registry was carried out according to all applicable national and local regulatory requirements. There was a regular review and verification of recorded data. From March 1, 2014, until December 31, 2019, patients were included. Data cleaning was performed thereafter, and final database lock was on October 31, 2021.

Totally 83 patients (57 females, 26 males) with MDS and del(5q) have been registered in 25 health care centers across Switzerland, which included minimum 1 and maximum 10 patients per center. The majority, 63 patients (75.9%), had a hemoglobin-level below 100g/L. At diagnosis of MDS, in all patients, a bone marrow (BM) aspirate (with dry tap in 8 patients), and in 78 patients (94%) additionally a BM biopsy was done. Conventional karyotyping was performed in 45 patients, both conventional karyotyping and fluorescence in situ

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hybridization (FISH) were performed in 26 patients, and in 12 patients only FISH was done. In 72 patients, there was exquisitely del(5q) detected. With regard to RBC-transfusion dependence (TD) at diagnosis, 41 patients (49.4 %) had RBC-TD with a median hemoglobin of 81 g/L (range, 50–110 g/L). In 55 patients (66.3%), the diagnosis was myelodysplastic syndrome with isolated del(5q) according to WHO Classification 2008. Prognostic stratification was done according to IPSS, IPSS-R, and WPSS (Figure 1A–C).

In total, 1714 cycles of treatment with lenalidomide were recorded. In all patients, at least one cycle of treatment with lenalidomide was given. At start of the first cycle, median hemoglobin was 87 g/L (range, 51–119 g/L), with 45 patients (54.2%) in need of RBC transfusions. Treatment with lenalidomide was initiated within 6 months after the diagnosis of MDS with a 5q deletion in 55 patients (66.3%).

With regard to onset and duration of treatment response, in cycle 2 of treatment with lenalidomide, 22 patients (26.5% of the total cohort and 48.8% of the patients with RBC-TD at treatment start) had RBC-transfusion independence (TI), another 5 (6% and 11.1%, respectively) each in cycle 3 and in cycle 4, 2 patients (3.6% and 4.4%, respectively) in cycle 5, and 1 patient (1.2% and 2.2%, respectively) in cycle 6. Of 61 patients with at least 6 documented treatment cycles 48 patients (78.7%) had RBC-TI for ≥ 8 weeks. Of those, 36 patients (75%) had a diagnosis of MDS with isolated del(5q). Analyzing those 61 patients with regard to erythroid response, there were 28 patients (45.9%) with RBC-TD and a hemoglobin < 90 g/L before start of treatment with lenalidomide, 16 patients (57.1%) had an erythroid response, that is, a reduction of at least 4 RBC transfusions with treatment with lenalidomide over a period of 2 months. In those 43 patients with at least 12 documented treatment cycles, 34 patients (79.1%) had RBC-TI for ≥ 26 weeks.

The recommended dosage of lenalidomide 10 mg daily on days 1–21 of a 28-day cycle was administered in 21 patients (25.3%) without adjustments. Venous thromboembolism prophylaxis was given in 33 patients (39.8%). Of note, there were 5 patients with a treatment-free interval (TFI) for various reasons and durations (Suppl. Table S1). There was a patient who had a complete cytogenetic remission after 6 and after 12 cycles of treatment with lenalidomide. Therefore, treatment was stopped with regular monitoring of blood count and del(5q) by FISH. This patient remains in complete hematologic and cytogenetic remission 3 years after stopping treatment.

Median overall survival (OS) in a multivariate analysis was significantly longer in patients who received no RBC transfusions during the first treatment cycle of 6.7 years (95% CI, 3.9–9.6) compared with patients who did receive RBC transfusions during that time of 3.34 years (95% CI, 2.56–4.12; $P = 0.014$), and was significantly longer in patients with MDS with isolated del(5q) of 6.7 years (95% CI, 3.0–10.4) compared with 2.4 years (95% CI, 1.99–2.9) in other entities of MDS ($P = 0.004$) (Figure 2A,B). With regard to Lenalidomide-emergent adverse events, there were no new safety signals identified.

In conclusion, treatment with lenalidomide was initiated within 6 months after the diagnosis of MDS with 5q deletion in about two-thirds of patients, reflecting the uncertainty with regard to the optimal time point to start disease directed treatment, especially in patients who are not—yet—RBC-transfusion dependent, as lenalidomide is formally approved only for patients with a transfusion-dependent anemia—and not for preventing it. In all patients, cytogenetic analysis at diagnosis was done. However, in 12 patients (14.5%), only FISH was performed at diagnosis, which is insufficient at initial work up. A minority of patients—14.5%—had higher-risk disease, and treatment with lenalidomide in this patient group would not entirely be in line with current guidelines. With the start of treatment with lenalidomide, 45 patients (54.2%) had RBC-TD, 22 of

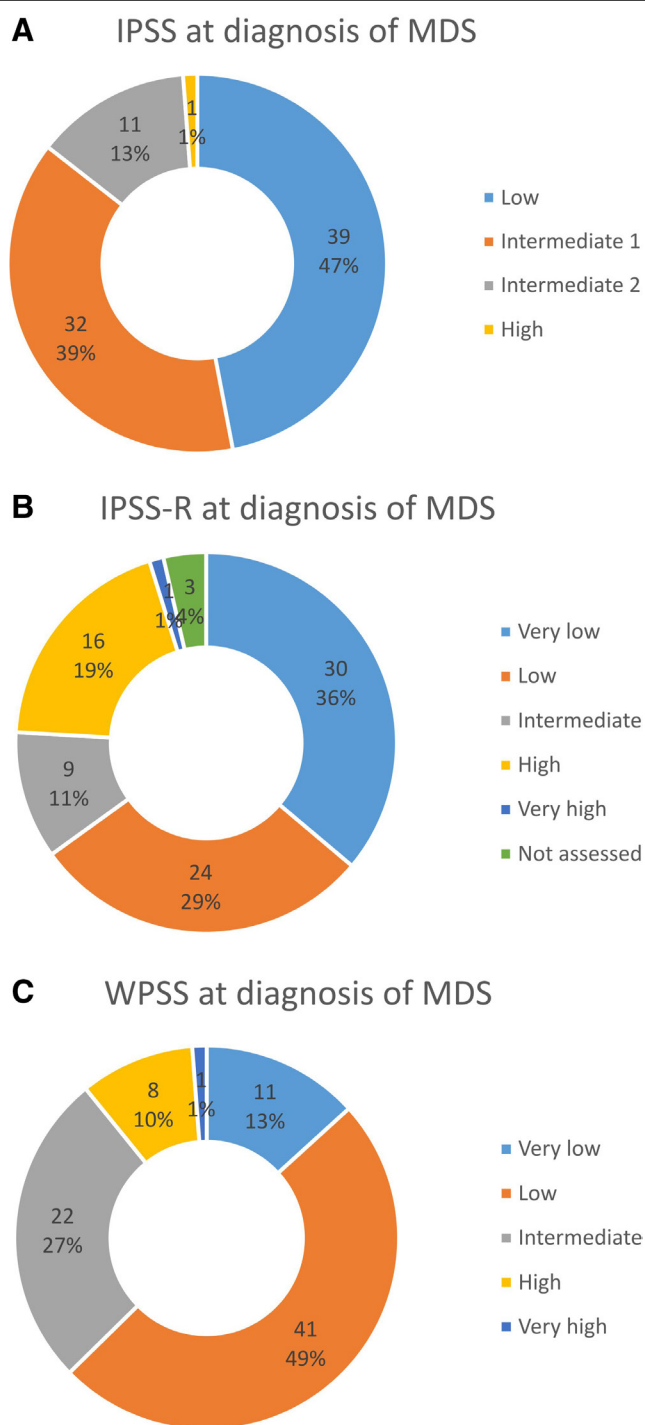


Figure 1. Prognostic scoring systems at diagnosis of MDS. (A) IPSS at diagnosis of MDS, (B) IPSS-R at diagnosis of MDS, and (C) WPSS at diagnosis of MDS. IPSS = International Prognostic Scoring System; IPSS-R = Revised International Prognostic Scoring System; MDS = myelodysplastic syndromes; WPSS = WHO Classification-based Prognostic Scoring System.

those patients (48.8%) were free of RBC transfusions in cycle 2, with 5 patients (11.1 %) each in cycle 3 and 4. This rapid onset of response and high efficacy with regard to RBC-TI is in line with the results of the MDS-003- and MDS-004-studies.^{5,6} Analyzing 61 patients with at least 6 documented cycles of lenalidomide treatment, RBC-TI for ≥ 8 weeks was more common in patients with a diagnosis of MDS with isolated del(5q) compared with other entities of MDS. Analyzing 43 patients with

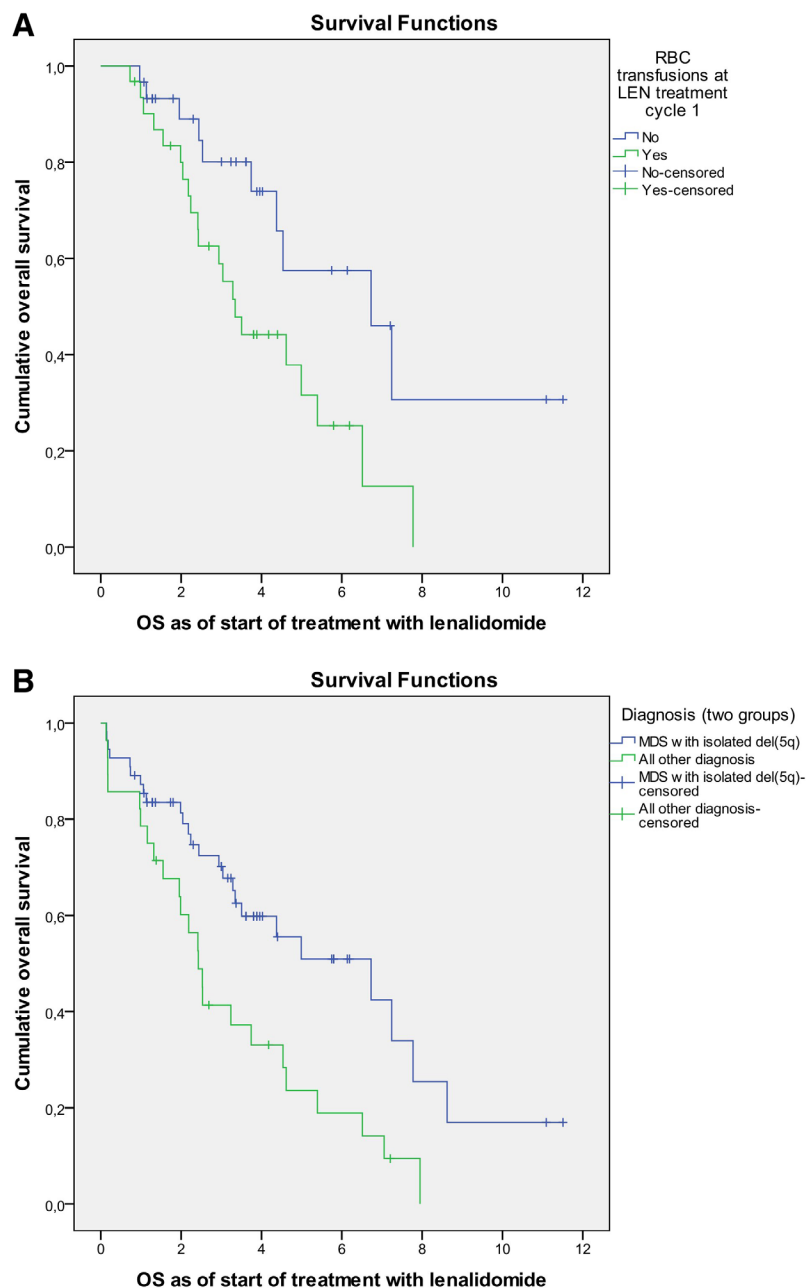


Figure 2. Median OS. (A) Kaplan-Meier curve for median OS as of start of treatment with lenalidomide according to RBC transfusions during cycle 1 of treatment with lenalidomide in 61 patients with at least 6 documented treatment cycles. There was a significant longer median OS in those 30 patients who received no RBC transfusions during the first cycle of treatment with lenalidomide of 6.7 y (95% CI, 3.9-9.6) compared with 31 patients who did receive RBC transfusions during that time of 3.34 y (95% CI, 2.56-4.12; $P = 0.014$). (B) Kaplan-Meier curve for median OS as of start of treatment with lenalidomide according to initial diagnosis of MDS. There was a significant longer median OS of 6.7 y (95% CI, 3.0-10.4) in those 55 patients with MDS with isolated del(5q) compared with 2.4 y (95% CI, 1.99-2.9) in 28 patients with other entities of MDS ($P = 0.004$). CI = confidence intervals; MDS = myelodysplastic syndromes; OS = overall survival; RBC = red blood cells.

at least 12 documented cycles of lenalidomide treatment, 34 patients (79.1%) had RBC-TI for ≥ 26 weeks. This confirms the high efficacy of lenalidomide with regard to RBC-TI in patients with MDS and 5q deletion also in daily clinical practice.^{5,6} Two months before start of treatment with lenalidomide, 25 patients (30.1%) of the whole cohort had no RBC-TD. Although off-label, commencing disease directed treatment at that time reflects daily clinical practice of not waiting for a patient with MDS to become RBC-transfusion dependent. Whether this practice will alter the natural course of the disease and has an impact on long-term outcome is not known, as is the optimal time of starting therapy. However, interim analyses of the SINTRA-REV trial (ClinicalTrials.gov Identifier: NCT01243476) in non-TD

LR MDS del(5q) patients suggest that early treatment with lenalidomide at low doses (5 mg) prolongs the time to and decreases the risk of TD with cytogenetic responses.⁷ This is supported by our data—although not corrected for disease duration and risk stratification—as patients with no RBC transfusions during the first cycle of treatment with lenalidomide had a significant improvement of median OS ($P = 0.014$).

Renal failure in this elderly population was the most prevalent condition and is possibly the explanation for the fact, that in only 21 patients (25.3%) the recommended lenalidomide dose was given without alterations. Diagnostic evaluation with BM analysis was done in about half of the patients who received 12 treatment cycles, in all other patients treatment with lenalidomide

was continued when peripheral blood values were (near) normal without morphological BM or cytogenetic response assessment. Response assessment beyond peripheral blood values seems to be of particular importance, as deep genetic responses are possible and could potentially lead to a treatment-free remission. Clarification on when and how response assessment has to be done is necessary. And there is a clear need for defining patient and disease characteristics with the possibility of a TFI.⁸ Median OS is significantly longer in lenalidomide-treated patients with MDS and isolated del(5q) compared with patients with other entities of MDS. This is longer compared with the MDS-004 study, which allowed recruitment of all subgroups of patients with MDS and del(5q), including patients with additional chromosomal abnormalities and blasts in BM of up to 10%, but all these patients had RBC-TD, which is in contrast to the SLIM-Registry.⁶ Observation time in our registry was too short to comment on the long-term safety of lenalidomide and on the possible occurrence of secondary malignancies. There is also a clear need for defining a diagnostic and therapeutic approach after stopping lenalidomide treatment due to intolerance or resistance to the drug with disease progression.

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AUTHORS CONTRIBUTIONS

AR and JSG designed the clinical data management application, performed research, and contributed as well as analyzed patient data. AR wrote the article. HA and NP developed, validated, and approved the clinical data management application and analyzed data. All authors performed research, contributed patient data, reviewed the article, and approved it for submission.

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