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LETTER TO THE EDITOR

Validation of the IPSS-R in lenalidomide-treated, lower-risk myelodysplastic syndrome patients with del(5q)

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Myelodysplastic syndromes (MDS) are a heterogeneous group of hematopoietic stem cell disorders with variable clinical outcome.[1–4] The International Prognostic Scoring System (IPSS) categorizes untreated MDS patients into one of four risk groups (low, intermediate [Int]-1, Int-2 and high) based on the percentage of bone marrow blasts, presence of cytogenetic abnormalities and number of cytopenias.[2] The revised IPSS (IPSS-R), also developed in untreated MDS patients, refines risk group definitions by assigning greater weight to the cytogenetic risk categories,[5] the depth of cytopenias and by altering bone marrow blast percentage cutoff points.[6] The IPSS-R assigns patients to one of five risk categories (very low, low, intermediate, high and very high) and has been validated by several groups.[7–9] The prognostic value of the IPSS-R in treated patients has not been fully established,[8–11] and its prognostic value specifically in patients with deletion 5q [del(5q)] treated with lenalidomide is unknown. We assessed the prognostic value of IPSS-R using data from two multicenter studies (MDS-003[12] and MDS-004[13]) that evaluated lenalidomide in red blood cell (RBC) transfusion-dependent patients with IPSS-defined low- or Int-1-risk MDS and del(5q), with or without additional chromosomal abnormalities.

Methods for the MDS-003 and MDS-004 studies have been previously described;[12,13] both studies were sufficiently similar to justify combined analyses. Patients received lenalidomide at doses of 5 or 10 mg/day for 28 days of each 28-day cycle, or 10 mg/day for 21 days of each 28-day cycle. This analysis included patients from MDS-003 and MDS-004 with available baseline IPSS[2] and IPSS-R[6] scores, who received lenalidomide from study start. IPSS-R adjusted for age (IPSS-R-A) was also calculated.[6] Risk groups with <5 patients were excluded. End points included overall survival (OS), time to progression to acute myeloid leukemia (AML) and rate of RBC transfusion independence (RBC-TI) $\geqslant$ 26 weeks. AML was defined by French–American–British criteria.[1] OS and time to AML were estimated using the Kaplan–Meier method, with differences evaluated using the log-rank test. Rates of RBC-TI $\geqslant$ 26 weeks were compared across risk groups using the Cochran–Armitage trend test. Univariate and multivariate Cox proportional hazards models were developed using the following covariates: IPSS (low-risk vs Int-1-risk), IPSS-R (multi-level), gender (female vs male), age (per year increase), French–American–British classification (refractory anemia (RA)/RA with ringed sideroblasts vs RA with excess blasts/chronic myelomonocytic leukemia), time since diagnosis (per year increase), transfusion burden (units/8 weeks), bone marrow blast count (as a continuous variable), bone marrow blasts ($<5\%$ vs $\geqslant 5\%$), number of cytopenias (as a continuous variable), number of cytopenias (0–1 vs 2–3), platelet count, absolute neutrophil count, hemoglobin (each analyzed as a continuous variable), del(5q) status (isolated vs $\geqslant 1$ additional abnormalities), RBC-TI $\geqslant$ 26 weeks response (yes vs no), RBC-TI $\geqslant$ 26 weeks response (time-varying; yes vs no), serum ferritin (per log unit increase) and serum lactate dehydrogenase (per unit increase). Significant variables identified by univariate analysis ($P \leqslant 0.10$) were used to develop multivariate models using SAS version 9.2; the best model was chosen using the Akaike information criterion. Data cutoff dates were 1 October 2010 for MDS-003 and 26 November 2012 for MDS-004.

Of the 286 lenalidomide-treated patients in MDS-003 and MDS-004, 201 had IPSS and IPSS-R scores available. Median age was 70 years (range 36–95), median time since diagnosis was 2.7 years (range 0.1–20.7) and most patients were female (72%). At baseline, patients received a median of 6 RBC units/8 weeks (range 1–25). Most patients had favorable disease characteristics: RA/RA with ringed sideroblasts (79%); 0–1 cytopenias (63%); isolated del(5q) (77%); and $<5\%$ bone marrow blasts (84%).

Overall, 83 patients (41%) had IPSS-defined low-risk disease and 118 (59%) had Int-1-risk disease. Using IPSS-R, 2, 55, 36, 7 and 1% of patients had very low, low, intermediate, high and very high-risk disease, respectively. A similar distribution was seen with IPSS-R-A, except that more patients were classified as very low risk (10 (5%) vs 3 patients (2%) with IPSS-R) because 8 younger patients in the IPSS-R low-risk group migrated to the IPSS-R-A very low-risk group. Of the 83 patients with IPSS-defined low-risk disease, 2 had very low risk (2%), 65 had low risk (78%) and 16 had intermediate risk (19%) by IPSS-R. Of the 118 patients with IPSS-defined Int-1-risk disease, 1 had very low risk (1%), 45 had low risk (38%), 57 had intermediate risk (48%), 14 had high risk (12%) and 1 had very high risk (1%) by IPSS-R. Baseline characteristics for the individual IPSS-R groups (low, intermediate, high), including IPSS score, transfusion burden, bone marrow blast count, number of cytopenias, platelet count, absolute neutrophil count, hemoglobin and cytogenetic complexity, were generally less favorable for patients in the higher IPSS-R risk groups.

OS was similar across IPSS-defined risk groups ($P = 0.50$; Figure 1a), but differed significantly across IPSS-R ($P = 0.01$; Figure 1b) and IPSS-R-A risk groups ($P = 0.02$; Figure 1c). In multivariate models, IPSS-R was independently associated with OS (low vs high; hazard ratio 0.45; $P = 0.02$), but IPSS was not (hazard ratio 0.97; $P = 0.87$). Other independent prognostic factors associated with improved OS included younger age, achieving RBC-TI $\geqslant$ 26 weeks and higher baseline platelet count.

For each prognostic system, 20–32% of patients progressed to AML across all risk groups. Time to AML progression was similar across risk groups by IPSS ($P = 0.29$), IPSS-R ($P = 0.30$) and IPSS-R-A ($P = 0.83$). The lack of difference in AML progression rates may be due to competing risks of death in an older patient population, which interceded prior to AML progression, or due to smaller sample size, which precluded adequate power calculations.

The proportion of patients achieving RBC-TI $\geqslant$ 26 weeks was similar across IPSS-defined risk groups ($P = 0.53$), but differed significantly across the low-to-high IPSS-R risk groups ($P = 0.03$) and the very low-to-high IPSS-R-A risk groups ($P = 0.03$) (Table 1).

In summary, compared with IPSS, IPSS-R demonstrated significant prognostic value for OS and rates of RBC-TI $\geqslant$ 26 weeks in RBC transfusion-dependent, lenalidomide-treated patients with IPSS-defined low- or Int-1-risk MDS and del (5q). This is likely due to its greater sensitivity to degrees of cytopenias and the relative weight of cytogenetic risk to

cytopenias accorded. It should be noted, however, that the total lenalidomide dose received and duration of treatment differed across the IPSS-R risk groups. In treatment cycle 1, the median total dose of lenalidomide was 210, 180 and 155 mg for the IPSS-R low-, intermediate- and high-risk groups, respectively, due to dose interruption and dose reduction. The median duration of

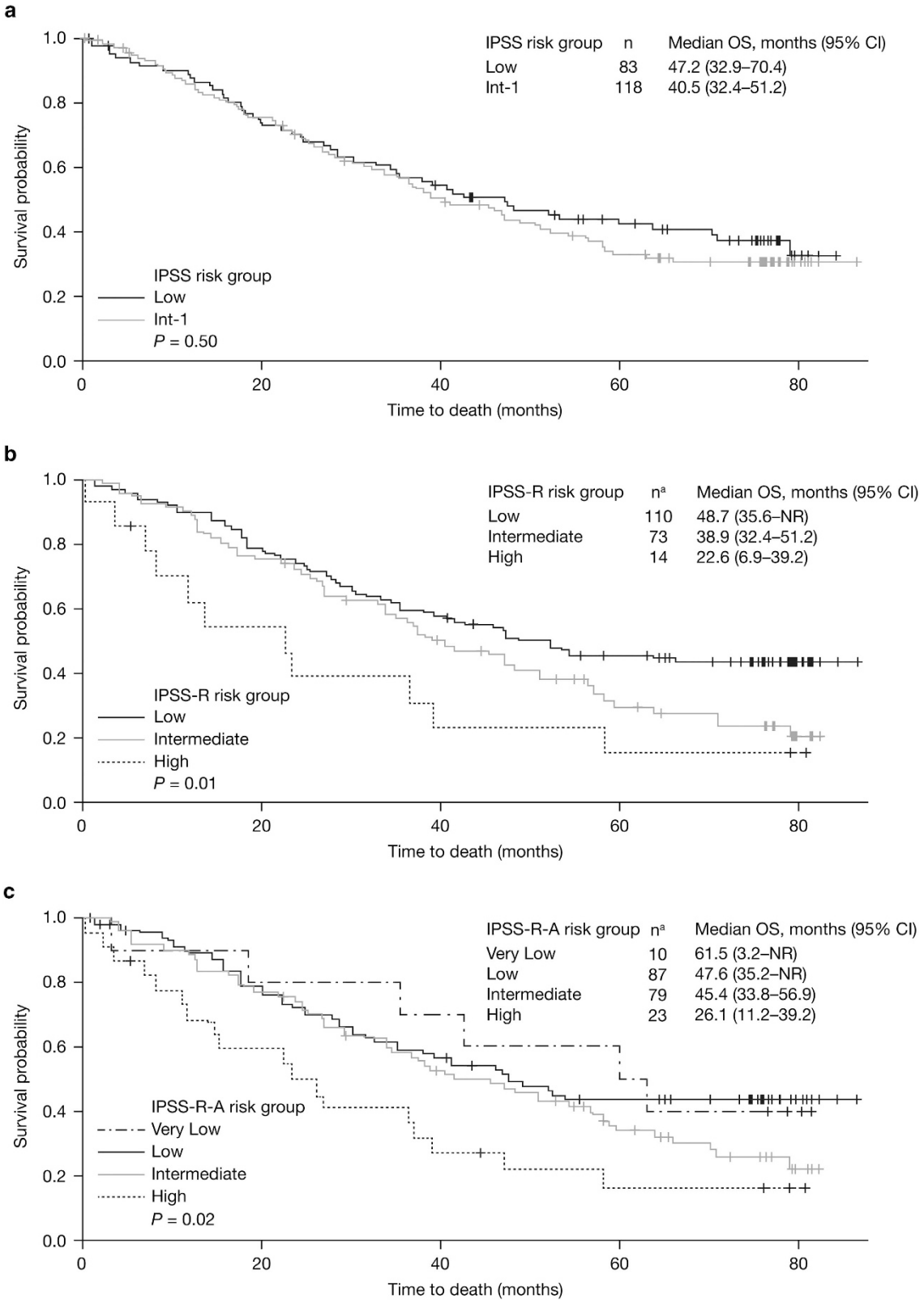

Figure 1. Kaplan–Meier curves showing OS according to IPSS (**a**), IPSS-R (**b**) and IPSS-R-A (**c**). [a]Risk groups with < 5 patients were excluded from the analysis. Abbreviations: CI, confidence interval; NR, not reached.

Table 1. Rates of RBC-TI ⩾ 26 weeks according to IPSS, IPSS-R and IPSS-R-A

Prognostic scoring system	*Risk group*[a]	*RBC-TI ⩾ 26 weeks*,[b] n/N *(%)*	P-*value*[c]
IPSS	Low	48/83 (57.8)	0.53
	Intermediate-1	63/118 (53.4)	
IPSS-R	Low	67/110 (60.9)	0.03
	Intermediate	39/73 (53.4)	
	High	4/14 (28.6)	
IPSS-R-A	Very low	8/10 (80.0)	0.03
	Low	51/87 (58.6)	
	Intermediate	42/79 (53.2)	
	High	9/23 (39.1)	

Abbreviations: IPSS, International Prognostic Scoring System; IPSS-R, revised IPSS; IPSS-R-A, IPSS-R adjusted for age; RBC-TI, red blood cell-transfusion independence. [a]Risk groups with < 5 patients were excluded from the analysis. [b]MDS-003 reported RBC-TI ⩾ 8 weeks; the current analysis of pooled data from MDS-003 and MDS-004 reports rates of RBC-TI ⩾ 26 weeks. [c]Cochran–Armitage trend test was used to evaluate linear trends for rates of RBC-TI ⩾ 26 weeks across risk groups for each prognostic scoring system.

treatment was 467, 365 and 118 days for the three IPSS-R risk groups, respectively, which reflects either better tolerability of lenalidomide for patients with lower-risk disease, or confounding by the IPSS-R group itself with respect to bone marrow reserve and natural history of disease. Neither IPSS-R nor IPSS was prognostic for AML progression, probably due to the small number of reported AML events and competing risks for death.

The prognostic value of IPSS-R has been assessed in MDS patients treated with other therapies, particularly hypomethylating agents, and in 1314 patients receiving best supportive care, induction chemotherapy or allogeneic transplantation, in whom it was superior to the World Health Organization Prognostic Scoring System in predicting OS;[8–11,14] however, this is the first study to validate the utility of IPSS-R beyond the initial MDS diagnosis in patients treated with lenalidomide. Similarly, the World Health Organization Prognostic Scoring System has been applied to an untreated population of 381 del(5q) patients and was found to be valid for predicting risk of AML transformation, highlighting the importance of transfusion dependency as a prognostic marker.[15] Although limited by its retrospective nature, the current analysis represents the largest available population of lenalidomide-treated patients with transfusion-dependent lower-risk MDS and del(5q). These results further support the use of IPSS-R as a validated prognostic tool in clinical practice.

CONFLICT OF INTEREST

MAS has received research funding from Celgene Corporation, and has served on the advisory boards for Celgene Corporation and Amgen. ASS, JSL, and MMS are employees of and hold equity in Celgene Corporation. PF has received honoraria and research funding from Celgene Corporation. GFS is on the advisory board of, and has received honoraria and research funding from, Celgene Corporation. FD has received honoraria from Celgene and Novartis. AFL is a consultant for and has received honoraria from Celgene Corporation. PLG and JMB declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Sekeres, Swern and Sugrue developed the concept; Sekeres and Sugrue wrote the manuscript; Swern and Li performed the statistical analyses; Sekeres, Fenaux, Greenberg, Sanz, Bennett, Dreyfus and List contributed to collection of data. All authors were involved in analyzing and interpreting the data and approved the final version of the manuscript.

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