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Prognostic relevance of cytogenetic systems in myelodysplastic syndromes

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We have read with great interest the recent article by Qu *et al.* [1] reporting the impacts of different cytogenetic categories in the Revised International Prognostic Scoring System (IPSS-R) on the prognosis of primary myelodysplastic syndromes (MDS).

Cytogenetic analysis has been recognized as an independent prognostic factor, and its inclusion within different systems has contributed to improvement in assessing the prognosis of MDS [2–4]. Stratifying cytogenetic findings in MDS started with counting the number of altered chromosomes as defined in the Lille system in 1993 [3]. The second published system was defined in 1995 as the Lausanne–Bournemouth index, which emphasizes the number of alterations [5]. In 1997, the IPSS recognized that the most frequent cytogenetic findings, such as −Y, 5q−, 20−, +8 and −7/7q−, belong to specific groups of risk, thus becoming the most widely accepted cytogenetic categories for assessing prognosis [2]. However, the IPSS included in the intermediate group a number of low-frequency cytogenetic alterations that make it heterogeneous, which is a matter of debate [4,6–8]. Later the IPSS was revised, and the risk of some less frequent cytogenetic findings was specified, dividing karyotypes into five categories (IPSS-R) [8]. Recently we have determined that the presence of an isolated deletion, excluding 7q−, is a good prognostic finding, while the presence of a monosomal karyotype (MK) is a high-risk marker (IPSS-MK). This system has shown independent prognostic impact and a better discriminating power compared with the IPSS categories [7]. MK refers to the presence of two or more distinct autosomal monosomies or a single monosomy associated with a structural abnormality [9]. Therefore, the aim of the present study was to compare these last two published cytogenetic stratifications, the IPSS-MK [7] and the IPSS-R [8], in a series of Argentine patients with MDS.

In this multicenter retrospective study we analyzed 518 patients with primary MDS (including 256 patients from the pilot study and MDS registry organized by the Argentine Society of Hematology) with available cytogenetic data, evaluated from September 1981 to April 2011. Clinical information and cytogenetic data concerning 421 patients have been previously reported [7]. All patients were categorized according to the French–American–British (FAB) system [10] and 433 patients were also evaluated according to the World Health Organization (WHO) 2001 classification [11]. The median age was 69 (14–93) years with a gender ratio of 1.4 (M/F: 301/217). During follow-up (median: 19 months, range: 1–266 months), 111 (21.4%) cases evolved to acute myeloid leukemia (AML) and 226 (43.6%) died (infections, bleeding and leukemic progression were considered as MDS-related causes of death), including 96 who had evolved to AML. Most patients received supportive care; chemotherapy was administered once the leukemic phase of the disease was confirmed (70 patients) or for stem cell transplant (18 patients, excluded from survival analysis); 76 patients received hypomethylating agents and 10 lenalidomide.

Among the overall 518 patients, 222 (43%) showed an abnormal karyotype. The most common cytogenetic aberrations in our series were: del(5q) (18% of 222 patients with abnormal karyotype; 5q − isolated: 19 cases, + other alteration: 21), −7/del(7q) (16%; isolated: 15, + other: 20), +8(21%; isolated: 26, + other: 21), del(20q) (8%; isolated: 14, + other: 4), +21(5%; isolated: 1, + other: 10), Y chromosome loss (8%; isolated: 14, + other: 3). Abnormal karyotypes showed one, two and ≥ three aberrations in 145 (66%), 33 (15%) and 41 (19%) cases, respectively.

The observed frequencies of abnormal karyotypes and of several cytogenetic alterations were similar to those in other

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Table I. Cross-tabulation of IPSS-R versus IPSS-MK*.

		IPSS-R					Survival	
Cytogenetic risk		Very good/good	Intermediate	Poor	Very poor	Total (%)	Events	Median (months)
IPSS-MK	Good	350	14	1	0	365 (71)	135	48.1
	Intermediate	5	73	4	0	82 (16)	44	28.0
	Poor	1	19	16	33	69 (13)	47	17.0
Total (%)		356 (71)	106 (21)	21 (4)	33 (6)	516		
Survival	Events	132	58	14	22			
	Median (months)	48.1	29.3	18.9	13.8			

*IPSS-R cytogenetic categories [8]: very good [del(11q) or −Y], good [normal, der(1;7), del(5q), del(12p), del(20q), or double including del(5q)], intermediate [−7/7q−, +8, i(17q), +19, +21, any other single, or any other double, independent clones], poor [der(3)(q21)/der(3)(q26), double including −7/7q−, or complex 3 abnormalities] and very poor (complex > 3 abnormalities). IPSS-MK cytogenetic categories [7]: good [normal, −Y, del(5q), del(12p), del(20q), other isolated deletions excluding del(7q)], intermediate (+8, any other single, or any other double, independent clones), poor [−7/del(7q), complex karyotype, MK].
IPSS-R, Revised International Prognostic Scoring System; IPSS-MK, International Prognostic Scoring System-monosomal karyotype.

reports [2–4,6,12,13]. The frequency of altered karyotypes varies in a wide range of 26–65% in different published MDS series. This variability may be related to difficulties in assessing and discriminating between regional variations or differences in classification, among others [7]. These epidemiological differences probably influence not only the percentage of abnormal karyotypes but also that of some cytogenetic findings, as observed by Qu *et al.* [1] regarding the reduced frequency of del(5q) and a higher frequency of trisomy 8.

Cytogenetic findings had a clear impact on the outcome of our patients. Those with abnormal karyotypes showed a significantly worse outcome than those with normal karyotypes, with a median survival of 26.4 vs 48.1 months, respectively ($p = 0.0002$). In our series, the subdivision of karyotypes according to either the IPSS-R [8] [Figure 1(a)] or IPSS-MK [7] [Figure 1(b)] systems confirmed significant differences in stratifying patients into cytogenetic groups of risk with different life expectancies (Table I). Similar results were obtained for both systems when patients receiving hypomethylating regimens were excluded (data not shown). Multivariate analysis showed that the IPSS-MK [7] categorization of karyotypes, where all isolated deletions were classified as "good" prognostic findings and MK among the worst, allowed us to better discriminate three groups of risk, compared with the IPSS-R distribution [8]. A Cox proportional hazards model using the "enter" method (SPSS software version 17) showed statistical differences between both systems ($p < 0.001$), and when the "backward stepwise" method was used to compare both systems the term IPSS-R was excluded from the final model (step 1: IPSS-MK: $p = 0.004$, IPSS-R: $p = 0.379$; final step 2 [IPSS-R removed] IPSS-MK: $p < 0.001$; Wald 52.746, Exp(B): 0.000, 0.285 and 0.402, respectively, for good, intermediate and poor cytogenetic groups of risk).

Cross-tabulation of both systems showed differences in the method of grouping several of the cytogenetic findings in our series (Table I). The IPSS-R [8] recognized that 11q − and 12p − alterations belong to either the very good or good risk group, in addition to –Y, del(5q) and del(20q) as accepted by

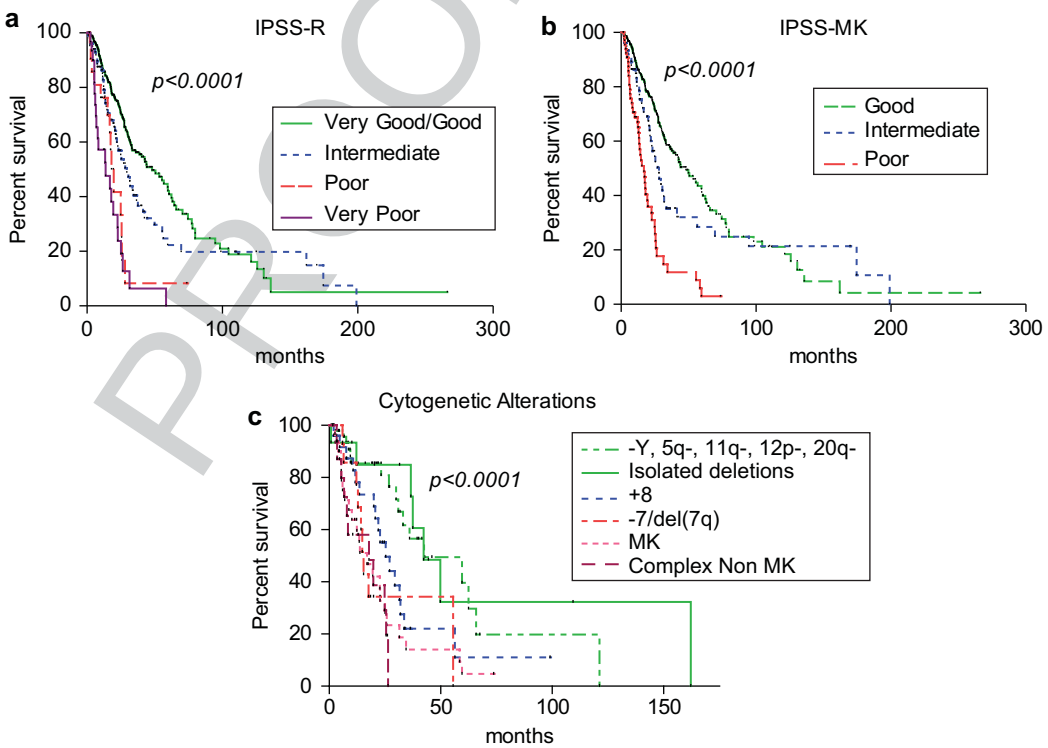

Figure 1. Kaplan–Meier survival curves for: (a) IPSS-R; (b) IPSS-MK; (c) cytogenetic alterations. Survival curves were calculated from the day of diagnosis and compared using the log-rank test (Mantel–Cox) provided by SPSS software (version 17.00) and plotted using GraphPad Prism (version 4.00).

the original IPSS [2]. According to the IPSS-MK, the presence of other isolated deletions (not including 7q −) is also considered a good prognostic finding [7]. In our series, 15 patients with isolated deletions showed a behavior similar to that of patients with good/very good alterations, with median survivals of 42.4 and 43.5 months, respectively [$p = 0.5538$, Figure 1(c)].

The intermediate group according to the IPSS-MK [7] is similar to the original IPSS [2] classification, albeit excluding isolated deletions and MK. The IPSS-R [8] excludes from its intermediate group the presence of a 5q − accompanied by other alterations (observed in five patients) and 3q rearrangements (observed in five patients), and includes the presence of an isolated − 7/del(7q). In our series, isolated − 7/del(7q) was observed in 15 patients and MK in 31 cases, with a median survival of 15.4 and 17 months, respectively, and no statistical differences were observed between them ($p = 0.8539$) [Figure 1(c)]. In addition, the IPSS-R defines poor and very poor risk groups [8], which showed, in our series, a median survival of 20 and 14 months, respectively [Figure 1(a)], without statistical differences between them ($p = 0.3592$), as was also observed by Qu *et al.* [1].

There is no doubt that the intermediate cytogenetic group according to the IPSS needs to be redefined. Our data regarding patients with − 7/7q − are coincident with the findings of Qu *et al.* [1]. Their patients showed a median survival of 14 months, very similar to our median survival of 15 months, while the median survivals for patients with trisomy 8 were 24.3 and 44 months for our series and that of Qu *et al.* [1], respectively. Both alterations are in the intermediate prognostic subgroup according to the IPSS-R criteria [8].

Cytogenetic findings had a clear impact on the clinical outcome in the present series, the largest in Latin America to our knowledge. The IPSS-MK, where three groups of risk have been identified, showed an independent prognostic assessment and a better discriminating power than the IPSS-R categories of risk in our population. It would be important to corroborate, in a larger group, our findings that all isolated deletions (excluding 7q −) are good prognostic findings and that MK is an indicator of poor prognosis.

The most frequent cytogenetic abnormalities (i.e. 5q −, 20q −, + 8) have been considered as risk indicators from the time that the original IPSS was published [2]. The presence of an isolated − 7/7q − is considered a poor-prognostic finding by the IPSS [2] and also by the GCEGCH (Grupo Cooperativo Español de Citogenética Hematológica) [4], WPSS (WHO prognostic scoring system) [12] and the MDACC (M. D. Anderson Cancer Center) [14] systems, among others. Although the IPSS-R was developed in a large series of 2901 patients [8], the researchers included a number of aberrations with a frequency below 0.7% (i.e. der1;7, rearr3q, 11q −, i17q and + 21) that were found in few patients not only in their series but also in ours. The low frequencies of these aberrations stress the importance of large study groups where their impact can be statistically evaluated. We agree with Qu *et al.* [1] in suggesting that the IPSS-R [8] should be confirmed in other large multicentric studies. In addition, new published data have confirmed the poor prognosis associated with MK in MDS [7,15], and we consider that MK should be included in the development of new cytogenetic systems.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal. [AQ4]

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