Leukemia Research 77 (2019) 8–13

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Research paper

Additional prognostic impact of the percentage of erythroid cells in the bone marrow of patients with myelodysplastic syndromes

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ARTICLE INFO

Keywords:
MDS
IPSS-R
AML
Erythroid precursors
Prognosis

ABSTRACT

In patients with myelodysplastic syndromes (MDS) the impact of the percentage of erythroid precursors in the bone marrow has been the subject of considerable debate, especially with regard to prognosis. We examined the prognostic impact of the percentage of erythroid cells in the bone marrow (bmery) in 2453 primary untreated MDS patients in a retrospective multi-center analysis. Bmery were quantified in bone marrow smears at the time of diagnosis and were correlated with overall survival (OS) and AML evolution.

We identified three distinct risk categories: "< = 10% bmery" (poor), "11–25 or > 45% bmery" (intermediate), and "26–45% bmery" (good) with distinct OS of 23, 40 and 48 months, respectively. The percentage of bmery showed prognostic significance concerning OS (Dxy = 0.08, $p < 0.001$) and AML-free survival (Dxy = 0.15, $p < 0.001$). Considering the IPSS-R by stratification, the Dxy were 0.09 for survival, and 0.18 for transformation ($p < 0.001$). Added to the IPSS-R, bmery enhances the prognostic power for both survival (Dxy = 0.39) and time to AML (Dxy = 0.59).

Survival and time to AML differ in MDS according to the percentage of bmery. The best outcome was found in those who had normal or near normal bmery counts. Moreover, adding bmery as differentiating feature to the IPSS-R may enhance its prognostic significance.

1. Introduction

Myelodysplastic syndromes (MDS) are neoplastic disorders of the hematopoietic stem cell characterized by dysplastic features of myeloid cells and various degrees of cytopenias. In a subset of patients, an increase in blast cells (< 20%) in the peripheral blood and/or bone marrow is found. MDS are diagnosed according to the World Health Organization (WHO) classification that has been revised several times over the past two decades. The current 2016 version as well as the formerly used 2008 WHO classification differentiate between MDS with normal bone marrow blast count and those with elevated bone marrow blasts [1,2]. In the groups of MDS with normal bone marrow blasts, the number of bone marrow cell lineages involved with dysplasia as well as the presence of ring sideroblasts, are key diagnostic markers.

Looking at the cellularity of the bone marrow, most MDS patients present with either a normocellular or hypercellular bone marrow [3,4]. About 40% of the patients present with erythroid hyperplasia that is defined as 33% or more red cells and is more frequently found in the subgroups with increased ring sideroblasts. In general, peripheral red cell numbers decrease with increasing dysplasia, but there is no direct correlation between the dysplastic features in the bone marrow as well as bone marrow cellularity with the degree of cytopenias in the peripheral blood in patients with MDS [4,5].

An important feature for diagnosis and for prognostication of MDS

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https://doi.org/10.1016/j.leukres.2018.12.012
Received 1 November 2018; Received in revised form 22 December 2018; Accepted 27 December 2018
Available online 28 December 2018

patients is the proportion of bone marrow blasts. Therefore, besides the karyotype, the percentage of bone marrow blasts as well as the number of cytopenias are considered in the International Prognostic Scoring System (IPSS) as well as in the revised IPSS (IPSS-R) [6,7]. In the current WHO classification, the amount of bone marrow blasts is counted on the basis of total nucleated cells [2]. In the 2008 classification, in case of ≥ 50% erythroid precursors among nucleated cells and > 20% bone marrow blasts in the non-erythroid cell population, the diagnosis erythroleukemia is appropriate (50% rule, for the first time proposed by the revised FAB classification in 1985 by Bennett et al.) [1,8]. Due to this recommendation, the impact of the percentage of erythroid precursors in the bone marrow has been the subject of considerable debate over the past several decades. In MDS with ≥ 50% BM erythroblasts (MDS-E) there is no consensus on the best method for enumerating BM blasts — from TNCs or from nonerythroid nucleated cells (NECs). Calculating the percentage of BM blasts from NECs may improve prognostic assessment of MDS [9] whereas others, including our own group of investigators, could not support this finding [10].

In the current WHO classification, the 50% rule has been removed. We therefore were interested in the prognostic impact of the percentage of erythroid precursors “per se” in the bone marrow (bmery) for all MDS patients and not only for those with elevated bone marrow blasts that may have been reclassified applying the 50% rule or not. We analyzed the prognostic impact of the amount of erythroid precursors in the bone marrow with regard to overall survival and AML evolution, both as single feature and in addition to the IPSS-R.

2. Material and methods

2.1. Patients

Data from 2453 primary untreated MDS patients from Germany, France, Italy, and Austria with available percentage of erythroid precursors in the bone marrow at the time of diagnosis were analyzed. Patients with chronic myelomonocytic leukemia (CMML) and erythroid leukemia, including M6 cases by FAB (now counting as MDS in the 2016 WHO classification) were excluded. All patients were classified according to the 2008 WHO classification. Patients with refractory cytopenia with unilineage dysplasia (RCUD), refractory anemia with ring sideroblasts (RARS), MDS with isolated deletion of. chromosome 5q (del(5q)) and refractory cytopenia with multilineage dysplasia (RCMD) were classified as low-risk MDS and patients with refractory anemia with excess blasts 1 and 2 (RAEB-1 and RAEB-2) are considered as high-risk MDS.

2.2. Statistical analysis

Overall survival and progression to AML were computed from the date of diagnosis. Patients were censored at the date of last follow-up. Censored data was described using the Kaplan-Meier method and differences between categories were tested by the logrank test. As a measure of prognostic power, the Dxy coefficient for censored data was used. Dxy is a concordance coefficient varying between -1 and 1, with 0 representing no predictive power and 1 perfect concordance of ascribed risk models.

All analyses were conducted with the statistics software R 3.4.3 (R Core Team), including the package "survival" [11,12]. Two-sided P values less than 0.05 were considered significant. In line with the essentially exploratory nature of the study, no adjustment for multiple testing was applied.

To examine the impact of the amount of bmery on survival and time to AML transformation, first the form of relation was examined by univariable and multivariable Cox models. For convenience bmery was then divided into four categories based on the resulting figures. To account for the U-shaped relation of bmery with risk regarding survival and time to AML transformation, the four categories were then reordered into "low", "intermediate", and "high risk", with "intermediate" comprising both, 11–25% bmery and > 45% bmery.

This risk related categorization was examined by univariable, as well as IPSS-R adjusted Kaplan-Meier curves, and by multivariable Cox models. While results from univariable analyses show the impact of bmery ignoring possible confounding by observed differences in known risk factors, adjusted curves and multivariable Cox models account for correlations between bmery and the IPSS-R, WPSS, and WHO. Adjusted curves offer the possibility to visually compare different bmery categories, as if each category would consist of the same proportions of IPSS-R risk groups, etc. Both adjusted curves and multivariable Cox models aim at the compensation for confounders to estimate the so called "independent" contribution of bmery.

To judge clinical relevance bmery was considered as a differentiating feature for the IPSS-R. Risk points were estimated for the risk categories of bmery and rounded for clinical convenience. These risk points were then added to the otherwise unmodified IPSS-R raw score and the resulting raw score was then categorized as defined in Greenberg et al. [7].

The Dxy's for survival and time to transformation of this bmery-differentiated-IPSS-R "IPSS-R(be)" were then compared to those of the plain IPSS-R. The "differentiating features"-approach was used because enhancing the IPSS-R that way by bmery keeps the calculation of the IPSS-R untouched but applies the differentiating risk points to the conventionally calculated raw score. Therefore, the scale of the IPSS-R remains unchanged, which means that comparisons between patients with available bmery data and others are reasonable. A total re-estimation of the weights for all IPSS-R features including bmery might have produced a somewhat better score, but one would have lost the possibility of easy comparison between risk assignments based on the IPSS-R and those based on the IPSS-R(be).

3. Results

3.1. Patient characteristics

The median age of the entire patient cohort was 73 years (range: 14–100 years). After a median follow up of 72 months, 1502 patients (61%) have died. At the time of data analysis, 282 patients (12%) showed a progression to AML. The distribution according to the WHO 2008 subgroups was RCUD 12%, RARS 13%, RCMD 41%, RAEB-1 15%, RAEB-2 14%, others 5%. Baseline characteristics are shown in Table 1.

3.2. Bone marrow erythroid precursors and peripheral blood counts

We determined correlations between the percentage of bmery and hemoglobin levels, ANC or platelet counts. The different values according to the percentage of bmery are shown in Table 1. Looking at the peripheral blood count, we could not find a correlation between the percentage of bmery and either hemoglobin levels, ANC, or platelet counts.

3.3. Overall survival and AML transformation

To evaluate the influence of the percentage of bmery on prognosis, we grouped the patients into those with < = 10% bmery, 11–25% bmery, 26–45% bmery and > 45% bmery. In univariable analyses, different median OS times were found in these four groups: OS for bmery < = 10% was 23.0 months, for 11–25% 39.9 months, for 26–45% 49.4 months, and for > 45% 41.5 months, respectively (Table 2). We also found a difference in the risk of AML evolution (Fig. 1). Median time to AML progression was not reached, therefore the 75%-quantiles were given. In patients with bmery < = 10% it was 46.0 months, for 11–25% 113 months, and for 26–45% as well as > 45% median time to AML progression was not reached (Table 2).

Therefore, the following three risk categories of erythroid cells were

Table 1
Baseline characteristics.

			erythroid cells in the bone marrow			
		All patients	< = 10%	11-25%	26-45%	> 45%
		n = 2453	n = 229	n = 689	n = 971	n = 564
	median age (range)	73 (14-100)	73 (17-92)	74 (20-100)	74 (20-100)	72 (14-95)
sex	male	1343 (55%)	126 (55%)	370 (53.7%)	534 (55.0%)	313 (55.5%)
	female	1110 (45%)	103 (45%)	319 (46.3%)	437 (45.0%)	251 (44.5%)
WHO	RCUD	290 (12.1%)	29 (13.8%)	91 (13.5%)	126 (13.3%)	44 (7.9%)
	RARS	307 (12.8%)	8 (3.6%)	33 (4.9%)	152 (16.0%)	114 (20.5%)
	RCMD	980 (40.8%)	77 (35%)	256 (37.9%)	388 (40.8%)	259 (46.7%)
	RAEB-1	367 (15.3%)	41 (18.6%)	137 (20.3%)	139 (14.6%)	50 (9.0%)
	RAEB-2	345 (14.4%)	55 (25%)	109 (16.2%)	102 (10.7%)	79 (14.2%)
	5q-	66 (2.8%)	7 (3.2%)	29 (4.3%)	22 (2.3%)	8 (1.4%)
	MDS-U	45 (1.9%)	3 (1.4%)	20 (3.0%)	21 (2.2%)	1 (0.2%)
IPSS-R n = 1245[a]	very low	222 (17.8%)	7 (6.7%)	62 (15.7%)	107 (21.0%)	46 (19.6%)
	low	498 (40.0%)	39 (37.1%)	157 (39.7%)	205 (40.3%)	97 (41.3%)
	int	299 (24.0%)	25 (23.8%)	113 (28.5%)	118 (23.2%)	43 (18.3%)
	high	151 (12.1%)	23 (21.9%)	46 (11.6%)	53 (10.4%)	29 (12.3%)
	very high	75 (6.0%)	11 (10.5%)	18 (4.6%)	26 (5.1%)	20 (8.5%)
Cytogenetic risk	very good	61 (4.9%)	4 (4.8%)	17 (4.3%)	28 (5.5%)	12 (5.1%)
(IPSS-R)	good	922 (74.1%)	72 (68.6%)	306 (77.3%)	377 (74.1%)	167 (71.1%)
	intermediate	170 (13.7%)	17 (16.2%)	50 (12.6%)	71 (14.0%)	32 (13.6%)
	poor	40 (3.2%)	4 (3.8%)	11 (2.8%)	17 (3.3%)	8 (3.4%)
	very poor	52 (4.2%)	8 (7.6%)	12 (3.0%)	16 (3.1%)	16 (6.8%)
blood count	Hb (g/L)	96 (22-175)	89 (43-149)	97 (32-175)	98 (22-169)	93 (42-169)
	ANC (G/L)	2.1 (0-53)	2.42 (0.06-26.2)	2.16 (0-23.7)	2.14 (0-23.6)	1.88 (0.05-53)
	Platelets (G/L)	152 (2-1530)	137 (3-898)	152 (2-1410)	163 (4-1190)	149 (2-1530)

[a] 1208 missing karyotypes.

defined: " < = 10%" (poor), "11–25 or > 45%" (intermediate), and "26–45%" (good). This categorization is motivated by the estimated risk regarding survival and time to transformation related to bmery (supplementary Fig. 1). For survival the three categories almost perfectly fit the four categories. Taking together "11–25%" and " > 45%" did not lead to any loss of prognostic power. Regarding time to AML "11–25%" seemingly shows lower risk than " > 45%", but in the interest of stability of the estimates and simplicity, we decided to use the same three categories for survival and time to transformation. This seems justified, as categories are in any case approximations for a seemingly continuous functional relation. Categorized that way, the number of erythroid cells in the bone marrow shows prognostic impact on survival (Dxy = 0.08, p < 0.001) and on time to AML progression (Dxy = 0.15, p-value < 0.001, Table 3, Fig. 2). When adjusting the curves for overall survival as well as for time to AML progression to the IPSS-R, the prognostic impact on survival and time to AML progression still remains significant (supplementary Fig. 2).

3.4. Bmery as a differentiating feature for the IPSS-R

As we could demonstrate an impact on OS as well as on AML transformation, we were interested, if the bmery can be used as an additional differentiating feature to improve the prognostic impact of the IPSS-R. Looking at the distribution of the bmery categories to the cytogenetic risk groups according to the IPSS-R (Table 1), it may be noted that relatively many patients in the extreme bmery categories (< = 10, > 45) have a complex karyotype categorized as "very poor" according to the IPSS-R. This is echoed also in the results for the detailed cytogenetic categories (supplementary Table 1). A complex karyotype is necessarily more frequent in the advanced categories, as this is equivalent to "very poor" cytogenetics. Del(5q) as well as trisomy 8 seemingly are negatively correlated with bmery, and normal karyotypes are remarkably less common in bmery < = 10.

Considering the IPSS-R (by stratified analyses), the Dxy was 0.09 for survival, and 0.18 for transformation, both with p < 0.001. Added to the IPSS-R, bmery slightly enhances the prognostic power for both survival (Dxy = 0.39) and time to AML (Dxy = 0.59). As with the differentiating features presented by Greenberg et al. [7] this is done by subtracting/adding from the raw IPSS-R score. In more detail, first the IPSS-R raw score is calculated in the standard way according to the published IPSS-R score. Then the respective weights for bmery risk categories are added (if > 25 to < = 45 the weight is -0.25, if 11–25 or > 45 it is 0.25, if < = 10 it is 0.75). This resulting raw score is then categorized according to the respective IPSS-R categories (very low < = 1.5, low > 1.5 - 3, intermediate > 3-4.5, high > 4.5-6, very high > 6). Fig. 3 indicates the respective IPSS-R categories without and

Table 2
Survival and time to AML by erythropoietic cells in the bone marrow.

	% bmery	n	events	median OS (months)	95% CI (months)	75%-quantile	
overall survival	< = 10	229	176	23	21-31	11.04	p < 0.001
	> 10- < = 25	688	381	38	32-46	15.64	
	> 25- < = 45	970	546	48	43-56	19.06	
	> 45	563	399	42	35-49	12.55	
AML progression	< = 10	229	46	n.r.	85-n.r.	46.23	p < 0.001
	> 10- < = 25	689	91	n.r.	n.r.	112.95	
	> 25- < = 45	968	78	n.r.	n.r.	n.r.	
	> 45	563	67	n.r.	n.r.	n.r.	

n.r. = not reached.

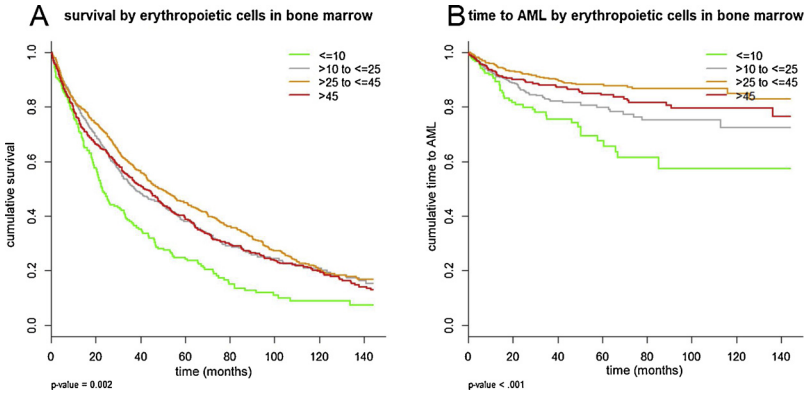

Fig. 1. Survival (A) and time to AML (B) by bmery (four categories).
A: Median overall survival times were 23 months for bmery < = 10%, 39.9 months for 11–25%, 49.4 months for 26–45%, and 41.5 months for > 45% 41.5, respectively (p = 0.002). B: Median time to AML progression was not reached, but the 75%-quantiles differed. In bmery < = 10% it was 46.0 months, for 11–25% 113 months, and for 26–45% as well as > 45% not reached, respectively (p < 0.001).

Table 3
Survival and time to AML by bmery risk categories.

	% bmery	n	events	median OS (months)	95% CI (months)	75%-quantile	
Overall survival	< = 10	229	176	23	21-31	11.04	p < 0.001
	11-25 or > 45	1251	780	40	35-45	13.63	
	> 25- < = 45	970	546	48	43-56	19.06	
AML progression	< = 10	229	46	n.r.	85-n.r.	46.23	p < 0.001
	11-25 or > 45	1252	158	n.r.	n.r.	136.25	
	> 25- < = 45	968	78	n.r.	n.r.	n.r.	

n.r. = not reached.

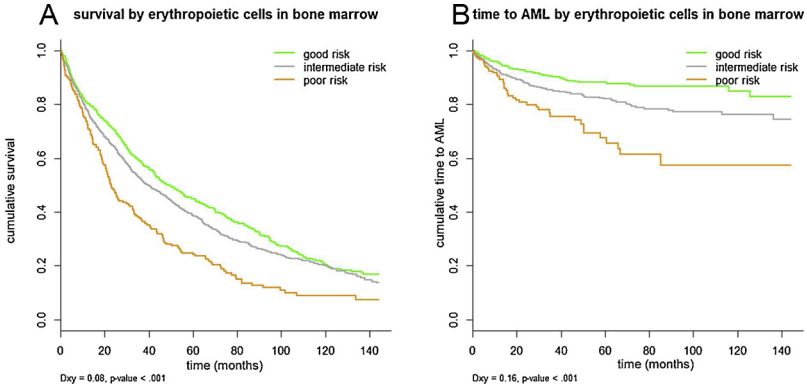

Fig. 2. Survival (A) and time to AML (B) according to the three risk groups.
A: Median times for OS were 23, 40, and 48 months for the poor, intermediate and good risk group, respectively (Dxy = 0.08, p < 0.001). Median time to AML progression was not reached, but the 75%-quantiles differed significantly with 46 months in the poor risk group, 137 months or the intermediate risk patients and was not reached in good risk patients (Dxy = 0.16, p < 0.001).

with the additional bmery categories. Bmery seems to be more important for time to AML progression, in particular in IPSS-R lower risk categories, but this interaction was not significant. On the other hand, subtracting the percentage of bmery from total nucleated cells when calculating the bone marrow blast percentage did not enhance the prognostic power of the IPSS-R. Dxy fall from survival: 0.37 and time to AML: 0.58 to 0.36, and 0.52, respectively.

4. Discussion

In this study, we analyzed the impact of bmery on prognosis in a larger cohort of patients with MDS. In accordance to a previous study [10], we could demonstrate the worst prognosis in the group of patients with a hypoplastic erythropoiesis in the bone marrow. In contrast to hypoplastic MDS, that are not associated with an inferior prognosis per se [13,14], a hypoplastic erythropoiesis has an adverse effect on patients´ outcome. Of note, we could demonstrate a non-monotone relation of bone marrow erythroid precursors with risk. We propose three different risk categories of erythroid precursors to account for the above mentioned none monotone relation with survival as well as with the risk of AML progression. Longest survival and time to AML progression are found at approximately the normal range of erythroid precursors in the bone marrow between 26% and 45%. Especially lower, and to a less pronounced influence higher percentages of erythroid precursors are slightly unfavorable, possibly reflecting a more disturbed hematopoiesis or a M6-like biology of the disease. This u-shaped relation has to be considered, when studying prognostic power. Although it was not the primary aim of our study to address the discussion on the 50% rule, our data support the decision of the current WHO classification to eliminate the nonerythroid blast cell count rule [2].

In accordance to previously published studies [4], we could not find a correlation between the percentage of erythroid precursors in the bone marrow and the cell counts in the peripheral blood. Although patients with very low and very high percentage of erythroid precursors seemed to have lower hemoglobin levels, there were no statistically significant differences. Obviously, low erythroid precursors in the bone marrow do not translate into low hemoglobin levels in the peripheral blood. The relationship between peripheral cell counts and disturbed hematopoiesis in the bone marrow of MDS patients is a complex interaction between the bone marrow microenvironment, apoptosis and genetic factors that promote the occurrence of MDS [15–17].

Adding bmery as a differentiating feature to the IPSS-R may enhance especially the prognostic power for time to AML in lower risk categories. When adding the related weights for bmery to the respective IPSS-R categories, it has the advantage that the impact is quantified on the level of the score, i.e. it is comparable to the weights of the IPSS-R

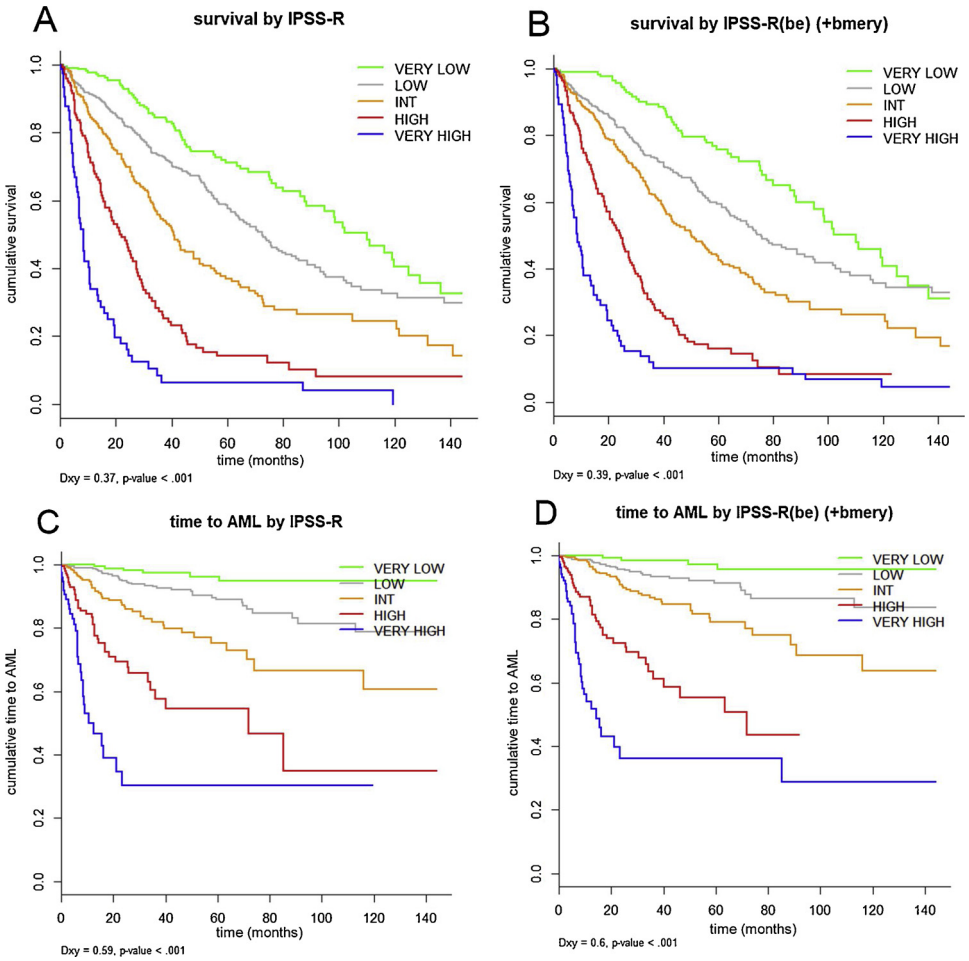

Fig. 3. IPSS-R without and with bmery as additional differentiating feature for OS and AML transformation.
Kaplan-Meier curves for overall survival (A, B) and time to AML progression (C, D) for each IPSS-R risk group without and with bmery. Added to the IPSS-R, bmery slightly enhances the prognostic power for both survival (Dxy = 0.39) and time to AML (Dxy = 0.6).

score components as given in Greenberg et al, 2012 [7]. The estimated risk difference between bmery in approximately the normal range (> 25%to < = 45%) versus 11%–25% or > 45% is 0.5, which is the same as the assigned risk difference of hemoglobin between 8 - < 10 g/dl versus < 8 g/dl, or ANC > = 0.8 versus < 0.8. In other words, when applying bmery to the raw data of the IPSS-R, it would have the same effect to change between hemoglobin 8- < 10 g/dl to hemoglobin < 8 g/dl, as it has to change from bmery > 25 to < = 45 to bmery 11–25 or > 45. Equally, a change from bmery 1–25 or > 45 to bmery < = 10 would result in the addition 0.5 to the raw score. In summary, our data support the view that bmery, categorized as we propose, would have an impact of half a point of the IPSS-R raw score. Our results suggest that the true influence of bmery is u-shaped, without any abrupt steps. Our results do not show that only < = 10% is unfavorable, while all other values are good risk. Also > 45% has an equal adverse effect on prognosis.

For survival, the finding of a very low or very high erythroid component would be similar to having either for example a poor ECOG performance status or an elevated LHD that would alter the IPSS-R by about 0.25 points [7]. Of note, in contrast to the differentiating features published by Greenberg et al. (performance status, serum ferritin, LDH, ß2-microglobulin), which are recommended only for risk determination regarding survival, bmery demonstrates some effect also on time to AML transformation. No enhancement was found for the WPSS. This may be caused by the different calculation of the WPSS, but it is also possible that bmery is already sufficiently well represented by the components of the WPSS (data not shown).

Looking at our data, one aspect may be a matter of discussion. In the group of bmery < 10%, we found a higher amount of patients with a high-risk MDS according to the IPSS-R with 21.9% and 10.5% IPSS-R high and very high risk, respectively (Table 1). Our stratified analyses show that < 10% bmery is unfavorable, even if accounting for IPSS-R risk groups, possibly reflecting a highly disturbed hematopoiesis resulting in an adverse prognosis associated with an advanced MDS subtype. Based on this observation one hypothesis would be that the development of erythroid precursors was suppressed by blast cells and other immature myeloid cells which would explain why low bmery patients have a poorer prognosis compared to patients with ´normal range´ bmery.

In summary, the percentage of bone marrow erythroid precursors can be used as an additionally tool to identify MDS patients at higher risk for progression and adverse prognosis and may be helpful for clinical decision making.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author's contribution

JMB helped with the design of the project and provided ongoing review of the manuscript. JN and HT prepared the original draft; HT provided the statistical analyses; PV provided helpful corrections for the

manuscript. All authors reviewed the final version.

Acknowledgement

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.leukres.2018.12.012.

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