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ORIGINAL ARTICLE

Myelodysplastic syndromes in adults aged less than 50 years: Incidence and clinicopathological data

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Summary

Purpose: *Myelodysplastic syndrome (MDS) is rarely seen in patients younger than 50 years, but rapidly increases with advancing age. Data on MDS biology in young patients are yet scarce but more than necessary. The purpose of this study was to estimate the proportion of MDS patients <50 years of age and to compare the clinicopathological data between younger and older patients.*

Methods: *Of our total MDS cases comprising 587 adult patients we studied 83 adults (14.14%) aged < 50 years with primary MDS.*

Results: *MDS patients were classified in those aged < 50 years and those aged ≥50 years. Younger MDS patients were characterized by female preponderance (p<0.001), better performance status (p=0.0035), less severe anaemia (p=0.008), better preserved kidney function (p=0.037), less often blast infiltration in bone marrow (p=0.015), more cases of RA (p<0.001) and RCUD (p=0.0066), lower MD Anderson score (p<0.001), longer overall survival (OS) (p<0.001), but similar progression rate (p=0.591). Median OS of young MDS patients was 39.7 months and 19 months of patients >50 years (p<0.001). In this group, 24 patients (28.92%) progressed to acute myeloid leukaemia (AML) vs 111 (22.02%) patients>50 years (p=0.402). Multivariate analysis identified platelet count (p=0.008) and percent of blasts in bone marrow (p=0.024) to be predictive for shorter OS in patients < 50 years of age; the same factors (p<0.001) together with IPSS-R cytogenetic risk group (p<0.001) were identified in patients >50 years of age. Platelet count (p=0.003) and percent of blasts in bone marrow (p=0.001) were predictive for higher risk of transformation to AML in patients <50 years, and bone marrow infiltration (p=0.022) and IPSS-R cytogenetic risk group (p=0.027) for patients >50 years of age.*

Conclusion: *Presenting features in young MDS patients may identify subjects at higher risk for unfavorable outcome.*

Key words: *clinical features, comparative study, myelodysplastic syndromes, prognosis, younger patients*

Introduction

The actual incidence of MDS is unknown. The incidence rates of MDS were not reported to the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Program (the United States Cancer Surveillance Program) until 2001 [1]. During the last two decades, a number of cancer registries have published data on the regional occurrence of MDS in Europe, suggesting that MDS is much more common than previously thought [2]. Estimates in Europe range from 3 to 20 cases per 100,000 [2,3], whereas in the United States, more than 10,000 new cases are diagnosed each year (median age 76 years) [1]. The incidence in men is significantly higher than in women (4.5 vs 2.7 per 100,000) [1]. The general assumption of the majority of hematologists is that MDS is rarely seen in patients younger than 50 years but

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increases rapidly with advancing age [3]. However, precise data on incidence of MDS in patients younger than 50 years are missing, as well as clinical and biological characteristics of such cases. To the best of our knowledge, only few papers are dealing with epidemiological [4] or clinicopathological data on MDS patients under 50 years of age [5-8].

In this paper, we focused on the estimation of the proportion of MDS cases < 50 years of age and their clinicopathological data. In addition, we compared these data with clinicopathological characteristics of MDS cases in patients older than 50 years of age.

Methods

We retrospectively studied 587 adult MDS patients diagnosed and treated between 1989 and 2011 at the three Hematology Departments in Serbia (Clinical Centre of Serbia, Belgrade, Clinical Centre of Vojvodina, Novi Sad and Medical Centre "Bezanijska Kosa", Belgrade). No specific informed consent could be obtained due to retrospective nature of the study. The study was performed in accordance with the Helsinki Declaration. The classification criteria were established according to FAB [9] and WHO classification [10]. Karyotypes were classified according to the International System for Cytogenetic Nomenclature Criteria [11] and international guidelines [12]. Data on the clinical outcome (death, survival, and development of AML) and other clinical and laboratory characteristics were collected from patients' medical files. The following parameters were assessed: age, sex, haemoglobin level, WBC count, ANC, platelet count, cytogenetic risk category, bone marrow aspirate blast percent, degree of marrow fibrosis (0-1 vs 2-3) [13], serum LDH (normal values defined by each hospital), ferritin, and red blood cell (RBC) transfusion dependence. The IPSS and IPSS-R were calculated according to Greenberg et al. [14-16], MD Anderson score according to Kantarjian et al. [17] and WPSS score according to Malcovati et al. [18].

Statistics

Numerical variables are presented in median values and ranges. Categorical variables are shown in counts and relative frequencies. OS was determined as the time between the date of diagnosis and the date of death or last follow up for censored patients. Time to AML transformation was defined as the time between the date of MDS diagnosis and the date of leukemic transformation or last follow up for censored patients. Survival was assessed using the Kaplan–Meier method and survival curves were compared using the log-rank test. Univariate and multivariate analysis were performed using the Cox proportional hazards regression model to identify significant independent prognostic factors. A p-value of <0.05 was considered to be statistically significant. Analyses were performed using the Statistica 10 software (Statsoft, Inc., Tulsa, USA).

Results

Patient characteristics

Among 587 adult patients with primary MDS, 83 patients were younger than 50 years. They accounted for 14.14% of our total MDS cases diagnosed during a period of 22 years. The median age of this group of patients was 38 years (range 18-49). According to FAB classification, the majority of them (44.6%) had refractory anemia (Table 1). According to WHO classification (patients were

Table 1. Distribution of morphologic subtypes in adult patients with primary MDS < 50 years of age and patients ≥50 years of age according to WHO classification (left) and FAB classification (right)

WHO classification	*All patients N (%)*	*<50 years N (%)*	*≥50 years N (%)*	*p value*	*FAB classification*	*All patients N (%)*	*<50 years N (%)*	*≥50 years N (%)*	*p value*
RARS	35 (6.0)	3 (3.6)	32 (6.35)	0.361	RARS	63 (10.7)	8 (9.6)	55 (10.91)	0.7949
RCUD	44 (7.5)	12 (14.5)	32 (6.35)	0.0066	RA	169 (28.6)	37 (44.6)	132 (26.1)	<0.001
RCMD-RS+ RCMD	128 (21.8)	23 (27.7)	105 (20.8)	0.11					
5q- Sy	12 (2.0)	4 (4.8)	8 (1.6)	0.07					
RAEB1	114 (19.4)	14 (16.9)	100 (19.8)	0.618	RAEB	206 (34.75)	20 (24.1)	186 (36.55)	0.413
RAEB2	100 (17.0)	9 (10.8)	91 (18.1)	0.136					
CMML1	44 (7.5)	6 (7.2)	38 (7.5)	0.986	CMML	69 (11.75)	8 (9.6)	61 (12.1)	0.1209
CMML2	18 (3.1)	1 (1.2)	17 (3.4)	0.3064					
RAEBT (AML)	67 (11.4)	6 (7.2)	61 (12.1)	0.459	RAEBT	80 (13.6)	10 (12.1)	70 (13.9)	0.7227
Unclassi-fied	21 (3.6)	5 (6)	16 (3.2)						

RARS: refractory anemia with ring sideroblasts, RCUD: refractory cytopaenia with unilineage dysplasia, RCMD: refractory cytopaenia with multilineage dysplasia, 5q-Sy:5q-syndrome, RAEB: refractory anemia with excess blasts, CMML: chronic monomyelocytic leukaemia, RAEBT: refractory anemia with excess blasts in transformation, AML: acute myeloid leukaemia

initially classified with FAB classification system since it was the official system till 2008, and re-classified according to known data, so categories as CMML1, CMML2, AML and unclassified were put into Table 1), the most frequent subtype in MDS cases aged < 50 years was refractory cytopenia with multilineage dysplasia (RCMD or RCMD-RS) with 27.7% cases, whilst 14.5% patients had RCUD, 16.9% had RAEB1 and 10.8% had RAEB2. In comparison to patients aged ≥50 years, in younger MDS patients there were more cases of RA (p<0.001) and RCUD (p=0.0066) (Table 1).

When comparing clinical features in MDS patients < 50 years of age vs patients ≥50 years, younger MDS patients were characterized by female preponderance (p<0.001), better performance status (p=0.0035), less severe anemia (p=0.008), better preserved kidney function (p=0.037), less often blast infiltration in bone marrow (p=0.015), lower MD Anderson score (p<0.001), longer OS (p<0.001), but similar progression rate (p=0.591) (Tables 2 and 3).

Cytogenetic analysis was assessed in 68 (81.93%) patients <50 years of age. Thirty eight (55.88%) exhibited karyotype abnormalities. Poor and very poor cytogenetics according to IPSS-R was present in 9 out of 68 cases (13.23%). In MDS cases aged ≥50 years karyotype abnormalities were found in 143 out of 346 available patients (42.11%). Poor and very poor cytogenetics according to IPSS-R was present in 49 out of 346 (14.16%) (p>0.05).

Outcome

Median OS for all patients was 21.9 months; for younger MDS cases it was 39.7 months, and for cases ≥50 years of age it was 19 months (p<0.001) (Figure 1). Among all patients, 137 (23%) progressed

Table 2. Comparison of clinical features in MDS patients < 50 years of age and patients ≥50 years of age

Clinical features	*All* *N (%)*	*< 50 years* *N (%)*	*≥50 years* *N (%)*	*p value*
Number	587	83 (14.14)	504 (85.86)	
Gender				0.0001
Female	237 (40.4)	48 (57.83)	189 (37.5)	
Male	350 (59.6)	35 (42.17)	315 (62.5)	
ECOG PS				0.0035
0,1	399 (67.97)	67 (80.72)	332 (65.87)	
2,3,4	55 (9.37)	1 (1.2)	54 (10.71)	
Missing data	133 (22.66)	15 (18.07)	118 (23.41)	
Hemoglobin (g/l)	85.29±22.1	91.27±23.29	84.30±21.77	0.008
Creatinine (mmol/l)	95.85±35.42	81.31±27.14	97.72±35.99	0.037
Bone marrow blast (%)	8.64±7.54	6.7±6.69	8.97±7.64	0.015
Platelet count (x10^9/l)	129±119	136.5±138	128±115	0.559
Neutrophil count(x10^9/l)	3.07±5.37	2.79±3.12	3.1240±5.67	0.617
WBC(x10^9/l)	6.85±13.18	6.61±11.34	6.8912±13.47	0.859
Ferritin (ng/l)	468±703	413±573	475±719	0.0779
Multilineage dysplasia				
No	103 (17.55)	22 (26.51)	81 (16.07)	0.0172
Yes	439 (74.79)	24 (65.06)	385 (76.39)	
Missing data	45 (7.67)	7 (8.43)	38 (7.54)	
Fibrosis (grade)				
0	333 (56.73)	57 (68.67)	276 (54.76)	0.7315
1	34 (5.79)	5 (6.02)	29 (5.75)	
2	22 (25.5)	21 (25.3)	1 (0.2)	
Missing data	198 (39.28)	0 (0)	198 (39.28)	
AML transformation				
No	380 (64.74)	56 (67.47)	324 (64.28)	0.4021
Yes	135 (23.0)	24 (28.92)	111 (22.02)	
Missing data	72 (12.26)	3 (3.61)	69 (13.69%)	

Table 3. Different prognostic scores used for comparison of MDS patients < 50 years of age and patients ≥50 years of age

Prognostic score	*All patients N (%)*	*< 50 years N (%)*	*≥50 years N (%)*	*p value*
IPSS				0.3941
Low	92 (15.67)	18 (21.67)	74 (14.68)	
Intermediate 1	160 (27.26)	29 (34.94)	131 (25.99)	
Intermediate 2	91 (15.5)	13 (15.66)	78 (15.48)	
High	59 (10.05)	6 (7.23)	53 (10.52)	
Missing data	175 (29.81)	15 (18.07)	158 (31.35)	
MD Anderson				<0.001
Low	108 (18.4)	38 (45.78)	70 (13.89)	
Intermediate 1	121 (20.61)	13 (15.66)	108 (21.43)	
Intermediate 2	75 (12.78)	7 (8.43)	68 (13.49)	
High	61 (10.39)	2 (2.4)	59 (11.71)	
Missing data	222 (37.82)	23 (27.71)	199 (39.48)	
WPSS				0.1255
Very low	47 (8.01)	13 (15.66)	34 (6.75)	
Low	67 (11.41)	13 (15.66)	54 (10.71)	
Intermediate	74 (12.61)	10 (12.05)	64 (12.7)	
High	121 (20.61)	21 (25.30)	100 (19.84)	
Very high	32 (5.45)	2 (2.41)	30 (5.95)	
Missing data	246 (41.91)	24 (28.92)	222 (44.05)	
IPSS-R				0.2403
Very low	38 (6.47)	8 (9.64)	30 (5.95)	
Low	105 (17.89)	24 (28.92)	81 (16.07)	
Intermediate	92 (15.67)	12 (14.46)	80 (15.87)	
High	97 (16.52)	13 (15.66)	84 (16.67)	
Very high	79 (13.56)	11 (13.25)	68 (13.49)	
Missing data	176 (29.98)	15 (18.07)	161 (31.94)	

For abbreviations see text

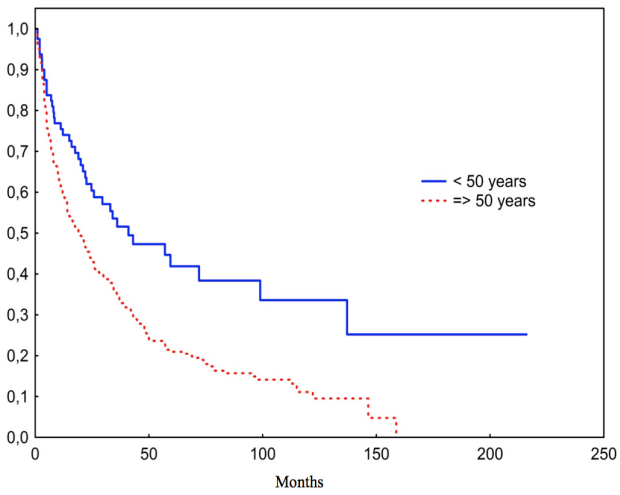

Figure 1. Kaplan-Meier plots predicting overall survival: MDS patients <50 years of age compared to patients ≥50 years of age (p<0.001)..

to AML. Among these patients, 24 were <50 years of age (28.92% of all younger patients).

Prognosis

Considering all MDS patients, multivariate analysis showed that hemoglobin concentration (p=0.008), platelet count (p<0.001), bone marrow blast infiltration (p<0.001), IPSS-R cytogenetic risk group (p<0.001) and age < 50 years (p=0.006) were independent risk factors for survival. Similarly, platelet count (p=0.037), bone marrow blast infiltration (p<0.001) and IPSS-R cytogenetic risk group (p<0.001) were identified as independent risk factors for AML transformation.

Table 4. Multivariate analysis of survival and AML transformation in MDS patients < 50 years of age and patients ≥50 years of age

Survival	*All patients p value*	*< 50 years p value*	*≥ 50 years p value*
Platelet count	<0.001	0.008	<0.001
Bone marrow blast infiltration	<0.001	0.024	<0.001
IPSS-R cytogenetic risk group	<0.001	NS	<0.001
< 50 years	0.006	NS	NS
Hemoglobin concentration	0.008	NS	NS
AML transformation			
Platelet count	0.037	0.003	NS
Bone marrow blast infiltration	<0.001	0.001	0.022
IPSS-R cytogenetic risk group	<0.001	NS	0.027

NS: non significant

Comparison of MDS patients <50 years of age with patients ≥50 years of age

Multivariate analyses identified similar features predictive for outcome and risk of transformation to AML in the two age groups (Table 4). Namely, platelet count and bone marrow blast infiltration were common risk factors in MDS patients <50 years of age for survival and AML transformation (p=0.008 and p=0.024 respectively, for survival, and p=0.003 and p= 0.001, respectively, for AML transformation) (Table 4). In MDS patients aged ≥50 years, independent risk factors for survival included platelet count (p<0.001), bone marrow blast infiltration (p<0.001) and IPSS-R cytogenetic group (p<0.001). For AML transformation, the same strength was found in bone marrow blast infiltration (p=0.022) and IPSS-R cytogenetic group (p=0.027) (Table 4).

Discussion

This study was designed to focus on the incidence and clinicopathological data of MDS patients younger than 50 years. The proportion of such patients in our study group was 14.14%, which is quite similar to the one reported in Romania, neighbouring country to Serbia [4], but twice as high than the proportion reported in Western countries [5,19].

In contrast to older MDS cases, younger patients exhibit female predominance, as already reported [4]. This fact is interesting since MDS is traditionally described as "elderly men disease". Younger patients had better performance status not only due to "lower burden of the years", but also due to less severe anemia and better preserved function of vital organs, particularly kidney function. Multilineage dysplasia and more intensive bone marrow blast infiltration were less common in younger MDS cases, suggesting more aggressive damage of hematopoietic stem cells in older cases. All these were the reasons for better OS in younger MDS cases in comparison to patients ≥50 years of age. Consequently, according to FAB and WHO classification, younger MDS patients had more RA and RCUD morphological subtypes than patients ≥50 years of age. It should be mentioned that RA according to the older FAB classification should be evaluated critically as in this classification MDS subtypes now classified as RCMD according to the WHO classification are included. Examination of the applicability of the various prognostic indices (i.e. risk models) to these two groups of patients showed that younger MDS patients have had lower MD Anderson prognostic score. However, such difference between the two age groups was not found when other risk models (IPSS, IPSS-R, WPSS) were used. The main reason why MD Anderson prognostic score was superior in differentiating the two age groups was the similarity of prognostic variables used in MD Anderson prognostic score (age, performance status, platelet count, bone marrow blast infiltration, WBC, cytogenetics, prior history of transfusions) and the prognostic variables found in our (uni) multivariate analyses. Namely, multivariate analyses identified platelet count and bone marrow blast infiltration as independent risk factors for OS in both age groups. IPSS-R cytogenetic risk group was additional predictive factor for OS in older age groups. Bone marrow blast infiltration was common independent risk factor for AML transformation in both age groups. IPSS-R was an additional predictive factor for AML transformation in older MDS patients, whilst platelet count was an additional predictive factor in patients < 50 years of age. We presume that much higher number of patients in the older group

than in the group of patients < 50 years of age can explain why IPSS-R cytogenetic risk group did not show prognostic significance in younger MDS patient group. In other words, while the IPSS-R score appears somewhat predictive for OS and AML transformation in older MDS cases, a larger number of younger patients need to be assessed to determine whether this system will be of prognostic utility in this patient population.

Among all studies on MDS patients aged <50 years or less reported so far [4-8], only Fenaux and colleagues [5] compared these patients with those aged >50 years. They found more cases of RAEB-T and less cases of RAEB and RARS, more frequent abnormal karyotype and monosomy 7, more frequent progression to AML (but identical OS) in younger adults with MDS, which results entirely contrast our results. However, owing to the fact that the study population in the Fenaux study has been derived from patients referred to centres that focus on bone marrow transplants, there may be a selection bias favoring referral of patients with more clinically aggressive disease by hematologists in the community [6].

In summary, clinical, pathological and cytogenetic features of primary MDS in younger adults are different than those in older patients, suggesting that this may represent a biologically different disease. Although younger MDS patients have had better prognosis in comparison to our older cases regarding OS, AML transformation rates were not different in our two age groups, indicating that bone marroe failure was the main cause of death in both age groups. However, suitability for allografting as well as lack of clinical trials with drugs which can change the natural history of the disease (5-Aza, lenalidomide) in our country still make prognosis in younger MDS patients poor. We hope that innovative treatment strategies and further molecular and biologic investigation will improve the prognosis of this cohort of MDS patients.

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