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Original Articles

Myelodysplastic Syndromes: FAB Classification, Age and Sex-related Incidence: An Emerging Pattern

Muhammad Javed Asif, Zafar Iqbal, Abdul Hayee, M. Farooq Alam
Department of Haematology, Shaikh Zayed Hospital, Lahore

SUMMARY

Myelodysplastic syndromes (MDS) are heterogeneous group of malignant disorders most commonly reported to affect the elderly people. In a retrospective analysis of 1546 consecutive patients entered in the bone marrow registry of Haematology Department, Shaikh Zayed Hospital, Lahore along six years (1994-1999), 35 cases of primary MDS were identified. Twenty six of these patients were male and 9 were female. All the 35 cases of MDS were analyzed to observe the pattern of age and sex incidence along with relative frequency of FAB subtypes. Overall mean age observed was 41.5 years. For the male patients the mean age was 44.9 years and 31.9 years for the females. Most common type of MDS observed was RAEB in 19 (54.3%), followed by RA in 9 (25.7%), RAEB-T in 4 (11.4%), CMML in 2 (5.7%) and RARS in 1 (2.9%).

INTRODUCTION

The myelodysplastic syndromes (MDS) are a group of heterogeneous clonal disorders of bone marrow characterized by refractory cytopenias in the peripheral blood and morphological evidence of marrow cell dysplasia involving at least two or generally three haematopoietic cell lineages[2,3,4]. Leukemic blast count is low in the bone marrow and peripheral blood[4]. Bone marrow is usually hypercellular[1,3,10]. Occasionally bone marrow may be hypocellular or even hyperfibrotic. These entities are now being considered as distinct morphological subgroups of MDS[5].

MDS are haemopathic malignant disorders affecting predominantly the elderly people. MDS are most commonly reported to occur in patients older than 60 years of age with a median onset in the seventh decade of life[3,22]. It is more common in men, particularly in older age group[7,17,19]. MDS is very rare in children and accounts for 1-2% of all leukaemias[4,9].

In the past this syndrome has been named as pre-leukaemia, smoldering leukaemia, oligoblastic leukaemia, dyshaemopoietic syndrome and dysmyelopoietic syndrome[1,10,11,15].

The initiation process of development of MDS is unknown. Pathogenesis of MDS is believed to be a multi-step or multihit process that involves two or more genetic alterations leading to emergence of an abnormal stem cell clone[23]. Haemopoietic stem cells are irreversibly altered and they produce the differentiated descendents that mature but yield end cells that are functionally and structurally defective[1].

As the incidence of MDS is reported to correlate strongly with age it is presumed that age dependent changes of the haematopoietic system may play a role in initiation of MDS, by rendering them particularly vulnerable to mutagenic insults[24].

Various karyotypic abnormalities are reported in MDS. In addition several immunological, proliferative and biochemical abnormalities associated with MDS support the assumption that haemopoietic dysplasias reflect a clonal abnormality at the level of the pleuripotent haemopoietic stem cell[13,14].

The natural history of MDS varies widely

ranging from chronic anaemia with low propensity for leukemic conversion to disorder characterized by profound disturbance in haematopoiesis and high risk of progression to acute leukaemia or bone marrow failure[13].

The French, American, British (FAB) classification system facilitates systematic analysis of these disorders. FAB classification first proposed in 1976 and later modified in 1982 defined five subtypes of MDS[11,12].

1. Refractory anaemia (RA) in which blast blood cells do not exceed 1% of the total count, and bone marrow shows hypercellularity with erythroid hyperplasia and less than 5% granulocytic blast cells;
2. RA with ring sideroblasts that account for more than 15% of all nucleated cells in the bone marrow;
3. RA with excess of blasts (RAEB) where circulating blast cells represent less than 5%, and the percentage of blast bone marrow cells is between 5% and 20%.
4. RAEB in transformation that include any of the following: more than 5% of blasts in the peripheral blood, more than 20% and upto 30% blasts in the bone marrow, and the presence of unequivocal Auer rods in the granulocytic precursors;
5. Chronic meylomonocytic leukaemia (CMML) defined by an absolute monocytosis (more than $1x10^9/l$), less than 5% peripheral blood blast cells, and a significant increase in monocyte medullary precursors accompanied by less than 20% blast cells in the bone marrow[14].

PATIENTS AND METHODS

This study was conducted in the Department of Haematology, Shaikh Zayed Hospital, Lahore. The study period extended from January 1, 1994 to December 31, 1999 (six years). A retrospective analysis was carried out on 1546 consecutive patients included in bone marrow study record of Haematology Department, along 6 years (1994-1999).

The patients who were analyzed and satisfied the FAB diagnostic criteria proposed for the diagnosis of myelodysplastic syndrome (MDS) were included in the study. All the patients included in the study represent primary MDS. Patients suffering from therapy related or secondary MDS were not included. MDS patients of all the age groups and both sexes were included.

Peripheral blood and bone marrow smears stained with routine Giemsa stain were re-examined to further confirm the diagnosis. Smears stained by special stains like Sudan black B, and myeloperoxidase were reviewed to confirm the granulocytic lineage of the blast cells. Bone marrow slides stained by Prussian Blue iron stain (Perl's reaction) were evaluated for the presence of ring sideroblasts and to confirm their percentage in each case.

All the patients diagnosed as "primary" MDS were subtyped according to the laid down criteria of FAB cooperative group[11,12,14]. These patients were further analyzed to observe the pattern of age and sex incidence along with relative frequency of various FAB subtypes.

RESULTS

Among the total of 1546 different patients registered along 6 years (1994-1999), 35 cases of primary MDS (2.3%) were identified. All the 35 MDS patients satisfied the FAB diagnostic criteria laid down for the diagnosis of myelodysplastic syndromes.

Males out numbered females with an overall male/female ratio of 2.9:1 (Table 1). Male / female ratio observed for different age groups was 2:1 for age 40 years and below, 6:1 for the age group of 41 to 50 years, 1.5:1 for the age group of 51 to 60 years and 5:0 for patients over 60 years of age (Table 3).

Overall age for all the MDS patients ranged from 9-78 years at the time of diagnosis with a mean and median age of 41.5 years and 40 years. For the male patients, mean and median age was 44.9 years and 45 years. For the female patients, mean and median age was 31.9 years and 26 years (Table 2).

Among the 35 patients 4 were children (11.43%), with a male to female ratio of 1:1. Eighteen patients (51.4%) were aged 40 years and below, 7 (20%) were 41-50 years of age, 5 (14.3%) were 51-60 years of age and 5 (14.3%) were above 60 years of age (Table 3) (Fig. 1).

Table 1: MDS. Male and female distribution (n=35).

Sex	*Number*	*Percent*
Male	26	74.3%
Female	9	25.7%
Total	**35**	**100.00**
Male/Female ratio:	2.9:1	

Table 2: MDS. Mean and median ages at the time of diagnosis (n=35)

	Range (Yrs)	*Mean age (Yrs)*	*Median age (Yrs)*
All patients (n=35)	9-78	41.5	40
Male (n=26)	12-78	44.9	45
Female (n=9)	9-60	31.9	26

Table 3: MDS. Pattern of age and sex distribution (n=35)

Age groups (Years)	*Number (n=35)*		*Male (n=26)*		*Female (n=9)*	
	No.	*%*	*No.*	*%*	*No.*	*%*
≤ 40	18	51.4	12	46.1	6	66.7
41-50	7	20	6	23.1	1	11.1
51-60	5	14.3	3	11.6	2	22.2
> 60	5	14.3	5	19.2		

MDS subtypes

Nine patients had refractory anaemia (RA) (25.7%), one patient had refractory anaemia with ring sideroblast (RARS) (2.9%), nineteen patients had refractory anaemia with excess of blasts (RAEB) (54.3%), four patients had refractory anaemia with excess of blasts in transformation (RAEB-T) (11.4%) and two patients had chronic myelomonocytic leukaemia (CMML) (5.7%) (Table 4).

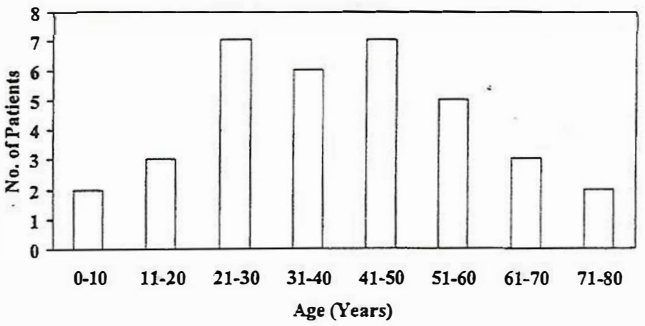

Fig. 1: Age distribution of MDS.

Table 4: MDS. Distribution of FAB subtypes (n=35).

Subtype	*Number*	*Percent*
RA	9	25.7
RARS	1	2.9
RAEB	19	54.3
RAEB-T	4	11.4
CMML	2	5.7

The distribution of various MDS subtypes in different age groups is summarized in Table 5. Among the 18 patients aged 40 years and below, 5 had RA (27.8%), 1 had RARS (5.5%), 9 had RAEB (50%) and 3 had RAEB-T (16.7%). Out of the 7 patients in age group of 41-50 years 2 had RA (28.6%) and 5 had RAEB (71.4%). Out of the 5 patients in age group of 51-60 years 2 had RA (40%) and 3 had RAEB (60%). Out of the 5 patients aged over 60 years 2 had RAEB (40%), 1 had RAEB-T (20%) and 2 had CMML (40%) (Table 5).

DISCUSSION

Among the total of 1546 different patients 35 cases of MDS (2.3%) were identified. This

frequency is low in comparison with two large studies conducted in Germany[7] and Spain[17] where the frequency of MDS was recorded upto 4.5% and 4.4% respectively among the patients included in the bone marrow study registries. Although this frequency does not reflect the true incidence of MDS in general population, yet it shows, that MDS are relatively less common in our population.

Table 5: MDS. Distribution of FAB subtypes in different age groups (n=35)

FAB Subtype	Age groups (Years) < 40		41-50		51-60		> 60	
	No.	%	No.	%	No.	%	No.	%
RA	5	27.8	2	28.6	2	40	-	-
RARS	1	5.5	-	-	-	-	-	-
RAEB	9	50	5	71.4	3	60	2	40
RAEB-T	3	16.7	-	-	-	-	1	20
CMML	-	-	-	-	-	-	2	40

Male to female ratio of 2.9:1 in this study reflects significantly higher male preponderance when compared with several international studies which report male/female ratio between 1:1 to 2:1. Most of the figures quoted are close to 1:1[16,19,22]. Male predominance is reflected in all the age groups, and is particularly more prominent in the age group of 41 to 50 years and in patients over 60 years of age (Table 3).

Overall mean and median age (Table 2) in our patients are much lower in comparison with the western countries where mean and median age of onset is usually more than 70 years[3,18,20,21,22]. Our figures are even lower than the mean age of 57.8 years reported for Central Africa[19] and median age of 56 years reported for Thailand[16].

The mean and median age for the female patients in this study is much lower as compared to the male patients. This may however not reflect the true picture as the number of female patients was rather small (Table 2).

Only 14.3% of our patients were over 60 years of age, whereas the proportion of the patients over 60 years of age is upto 80% or more as reported in Western studies[7]. Majority of our patients are aged 50 years or less and significantly large number of our patients are 40 years or less at the time of diagnosis. It is in sharp contrast to the western population where MDS are reported to be rare below 50 years of age[1]. In one large German study it is reported to be 6.7% in this age group[7]. This observation probably reflects a definite pattern. The myelodysplastic syndromes appear to affect considerably younger population in our set-up.

Most common sub-type of the MDS observed was RAEB, followed by RA, RAEB-T, CMML and RARS. In the international studies there is a marked variation in the reported relative incidence of various subtypes of MDS[16,19,21]. In a pooled data analysis the percentage ranges for RA is 8-43%, for RARS 2-37%, for RAEB 13-38% for RAEB-T 4-27% and for CMML 1-32%[22]. In our study comparable results are obtained as far percentage ranges for all the various subtypes of MDS are concerned, except in case of RAEB which shows a much higher incidence in our patients.

FAB type distribution in different age groups shows that RAEB is the commonest type in all age groups except in patients over 60 years of age where its relative frequency is equal to that of CMML.

RAEB and RAEB-T constitute 68% of the total 25 MDS cases aged 50 years and below (Table 5). The overall pattern of FAB type distribution suggests that more aggressive forms of MDS are relatively more frequent in younger patients.

CONCLUSION

- Myelodysplastic syndromes (MDS) which are primarily considered as disorders predominantly affecting elderly people appear to affect considerably younger people in our population.
- There is a distinct male preponderance.
- Most of the younger patients present with relatively more aggressive forms of MDS.

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The Authors:

Muhammad Javed Asif,
Assistant Professor
Department of Haematology,
Shaikh Zayed Hospital,
Lahore.

Zafar Iqbal,
Demonstrator
Department of Haematology,
Shaikh Zayed Hospital,
Lahore.

Abdul Hayee
Professor
Department of Haematology,
Shaikh Zayed Hospital,
Lahore.

M. Farooq Alam
Pathologist
Ittefaq Hospital
Lahore.

Address for Correspondence:

Muhammad Javed Asif,
Assistant Professor
Department of Haematology,
Shaikh Zayed Hospital,
Lahore.