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Cytogenetic characteristics in Vietnamese patients diagnosed with primary myelodysplastic syndromes☆

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ABSTRACT

Background: The karyotype is the important factor for the diagnosis and prognosis of *primary myelodysplastic syndromes* (*MDS*). Some previous studies have suggested that the incidence of chromosomal variations in MDS was related to race. We analyze the *chromosomal characteristics* in *Vietnamese patients with MDS* to find differences compared to other races and the association with subtypes by WHO classification.
Methods: Sixty patients with new primary MDS diagnoses underwent cytogenetic analysis and FISH for del(5q).
Results: Twenty-five patients (41.67%) had an abnormal karyotype at the time of diagnosis, in which 18 patients with a complex karyotype (≥3 chromosomal abnormality) represented the highest percentage (30%). The most frequent chromosomal abnormalities were +8 found in 10/60 patients (16.7%), del (5q) in 9/60 patients (15%), -18 in 5/60 patients (8.3%), only one patient had isolated del(5q) with 1.67%. Patients with abnormal karyotype had higher odds of being MDS-EB (MDS with excess blast) compared to those with normal karyotype (OR = 3.407, 95% CI = 1.164 – 9.976). Patients with complex karyotypes had a higher probability of having MDS-EB compared to those without complex karyotype (OR = 3.25, 95% CI = 1.018 – 10.379).
Conclusions: The complex karyotype was the most frequent chromosomal abnormality. Patients with an abnormal or complex karyotype had a higher probability of having MDS with excess blast. The isolated del (5q) ratio is very low compared to Europe and North Africa, but similar to China and Japan as they are the same countries in East Asia.

1. Introduction

Myelodysplastic syndromes (MDS) are a group of heterogeneous hematopoietic stem cell disorders characterized by ineffective hematopoiesis, bone marrow dysplasia, and peripheral cytopenia with increased susceptibility in transformation to acute myeloid leukemia [1]. In approximately 50% of patients with MDS, cytogenetic abnormalities are detectable by conventional chromosome analysis from bone marrow metaphases [2]. Cytogenetic abnormalities play an important role in the diagnosis, classification, prognosis, and therapy of MDS, so chromosome analysis is essential.

Cytogenetic abnormalities have become one of the diagnostic criteria that define MDS. According to NCCN, the diagnosis of MDS requires ≥1 of 3 following MDS-related criteria: (1) dysplasia (≥ 10% in ≥ 1 of 3 major bone marrow cell lines); (2) blast cells percentage of 5 – 19%; and (3) a specific MDS-associated karyotype {eg, del(5q), del(20q), +8, or del (7)/ del(7q)} [3]. Cytogenetic abnormalities were also part of the minimal diagnostic criteria of the MDS proposal proposed by WHO from 2001 to 2007 [4].

The MDS classification has improved and changed several times for decades. In 1982, the FAB classification was based on percentage of blasts and morphological features in blood and bone marrow, ringed sideroblasts, and number of monocytes in peripheral blood. In 2001, the WHO proposed a classification for MDS that was modified from the original French-American-British (FAB) definitions and from there MDS-isolated 5q- has become one of the important suptypes of MDS. Since then, this classification has been updated twice (2008 and 2016). The 2016 WHO classification defined one type of unclassifiable MDS (MDS-U CG) based on defining the cytogenetic abnormality [3,5,6].

Cytogenetic abnormalities have been considered a factor in the calculation of the MDS risk score. The prognosis of MDS is calculated using the International Prognostic Scoring System Revision (IPSS-R)

☆ This study was carried out at the Center of Hematology and Blood Transfusion, Bach Mai Hospital, 78 Giai Phong Street, Hanoi, Vietnam

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score, which includes categories analysed for cytogenetics, in addition to the number of cytopenia and the blast percentage. The present of >3 chromosomal abnormalities indicates a very poor prognosis [3,6].

Cytogenetic abnormalities also play an important role in the selection of the most effective therapy. Lenalidomide is the FDA- approved standard of care for low-risk MDS with del(5q), capable of inducing cytogenetic CR and achieving transfusion independence [7,8].

Although cytogenetic findings are not used to outline specific subtypes of MDS, except for some special suptypes (MDS-U CG, MDS isolated del(5q) for example), they were strongly correlated with a prognosis.

With such important implications, some studies also suggested that chromosomal characteristics in patients with myelodysplastic syndromes were race-related, which may affect the diagnosis of some special suptypes, as well as prognosis. Yasser Elnahass et al., indicated that the cytogenetic characteristics of Egyptian patients with MDS were similar to those of North African and European patients, Akira Matsuda et al., showed that the prognosis of Japanese patients was significantly more favorable than that of German patients [9,10].

The present study was conducted to analyze the cytogenetic characteristics in Vietnamese patients with primary MDS to find differences compared to other races and the association with subtypes by WHO classification.

2. Patient and methods

2.1. Patients

A total of 60 patients with primary MDS diagnosis new in the Center of Hematology and Blood Transfusion – Bach Mai Hospital, Hanoi, Vietnam, in the period between January 2018 and September 2020 were enrolled in our study.

2.2. Conventional cytogenetic analysis and fluorescence in situ hybridization

Chromosome analysis was performed on bone marrow aspirate specimens of 60 patients with primary MDS at the time of diagnosis. Bone marrow samples were processed after culture (24) following standard procedures. Chromosomes were stained with G bands, and karyotypes were reported according to the recommendations of the International System for Human Cytogenetic Nomenclature (ISCN, 1995) [11]. All samples were subjected to fluorescence *in situ* hybridization (FISH) studies for del(5q).

2.3. Definitions

Morphological assessment for the diagnosis of MDS, defining cytopenia, rating of dysplasia, and blasts percentage was performed according to the criteria of IWGM-MDS 2008 and the WHO 2016 criteria [12,3,6]. Cytogenetic abnormalities used to define MDS were according to WHO 2016 criteria [3,6]. The diagnosis of MDS was by Proposal of minimal diagnostic criteria of MDS [4]. The classification of MDS of the patients in our cohort was based on WHO 2016 [3,6]. IPSS-R was utilised as a prognostic tool [3,6].

2.4. Statistical analysis

Numerical data were offered as mean and range as appropriate. Qualitative data have been expressed as frequency and percentage. Differences in the distribution of variables among subsets of patients were analysed using χ^2 and Fisher's exact tests. The ORs were calculated to understand the association between the abnormal karyotype or complex karyotype with the MDS- EB status (MDS with excess blast).

The study protocol was approved by the Ethical Committee in Hanoi Medical University. Patient consent was waived by the committee as this study was a retrospective observational study.

Table 1
Patients characteristics.

Age (years)	Mean	60.38 years
	Min-max	16–86
Gender (n,%)	Male	36 (60%)
	Female	24 (40%)
Hemoglobin (g/L)	Mean	79.80
	Min-max	35–130
Total neutrophil count ($\times 10^9$/L)	Mean	4.2
	Min-max	0.04–75
Platelet count ($\times 10^9$/L)	Mean	79.0
	Min-max	2–653
Peripheral blood Cytopenias (*n*, %)	Unicytopenia	14 (23.3%)
	Bicytopenia	22 (36.7%)
	Pancytopenia	24 (40.0%)
Peripheral blood Blast (%)	Mean	2
	Min-max	0–18
Total bone marrow cell count ($\times 10^9$/L)	Mean	65.62
	Min-max	4.27 _ 514
Bone marrow cellularity (*n*,%)	Hypercellular marrow	9 (15%)
	Normocellular marrow	30 (50%)
	Hypocellular marrow	21 (35%)
Bone marrow Blasts (%)	Mean	9.76
	Min-max	0–18
MDS subtypes (*n*,%)	MDS-SLD	9 (15.0%)
	MDS-MLD	22 (36.67%)
	MDS-EB1	9 (15%)
	MDS-EB2	19 (31.67%)
	Isolated del (5q)	1 (1.67%)
Karyotype	Normal	35 (58.33%)
	Abnormal	25 (41.67%)
	Single chromosomal abnormality	4(6.67%)
	2 chromosomal abnormality	3 (5.0%)
	≥3 chromosomal abnormality	18 (30.0%)
Risk categories (IPSS-R)	Very low	2 (3.33%)
	Low	15 (25%)
	Intermediate	11 (18.33%)
	High	12 (20%)
	Very high	20 (33.33%)

3. Results

3.1. Clinical data

At diagnosis, there were 60 patients: 36 were males, with a mean age of 60.38 y (range: 16–86). Twenty- two patients were diagnosed with MDS-MLD, accounting for the highest rate (36.67%), only one patient was diagnosed with MDS- isolated 5q-, accounting for the lowest rate (1.67%), other forms included MDS-SLD, MDS-EB1 and MDS-EB2. According to IPSS -R, the group of patients with very high risk accounts for the highest proportion (33.33%), the group with very low risk accounts for the lowest percentage (3.33%) (Table 1).

3.2. Chromosome analysis

Chromosome analysis and fluorescence in situ hybridization for del (5q) was available in 60 patients and 25 patients (41.67%) had an abnormal karyotype at the time of diagnosis, in which 18 patients with complex karyotype (≥3 chromosomal abnormality) represented the highest percentage (30%) (Table 1).

The most frequent chromosomal abnormalities were +8 in 10/60 patients (16.7%), del (5q) in 9/60 patients (15%), -18 in 5/60 patients (8.3%), but only one patient had isolated del(5q) and only one patient

Table 2
Abnormal cytogenetic features in 25 primary MDS patients.

Delete (21)		Duplication (12)		Loss chromosome (40)		Gain chromosome (82)		Translocation (7)		Others (19)	
	f		*f*		*f*		*f*		*f*		*f*
del(5q)	**9**	dup1q	1	2	2	1	4	t(1;7)	1	hyper	3
del(6q)	3	dup7p	1	3	1	2	3	t(1,8)	2	dic (3;9)	1
del(12p)	1	dup7q	1	4	1	3	3	t(1,9)	1	dic(12;18)	1
del(13p)	2	dup10q	2	5	5	4	3	t(3;10)	1	i(5p)	1
del(14p)	2	dup14q	2	6	1	5	4	t(6;12)	1	inv (3)	1
del(17p)	1	dup17p	3	7	4	6	4	t(17;20)	1	der 9	1
del(18 q)	1	dup17q	1	9	1	7	3			der 12	1
del(19 q)	1	dup20q	1	11	1	**8**	**10**			mar	10
del(20p)	1			12	1	9	3				
				13	1	10	3				
				14	1	11	5				
				15	3	12	3				
				18	**5**	13	3				
				19	1	14	3				
				20	1	15	2				
				21	4	16	3				
				22	4	17	3				
				Y	3	18	5				
						19	3				
						20	3				
						21	4				
						22	3				
						X	2				

Note: Only one case of del(5q) was a isolated chromosomal abnormality, the remaining 8 case were complex karyotype.

Table 3
Cytogenetic profile with suptypes in 60 MDS patients.

Primary MDS types	Abnormal karyotype (n,%)	Normal karyotype (n, %)	P
MDS-SLD (n = 9)	1 (11.1%)	8 (88.9%)	0.044
MDS- MLD (n = 22)	7 (31.8%)	15 (68.2%)	0.239
MDS-EB1 (*n* = 9)	7 (77.8%)	2 (22.2%)	0.027
MDS-EB2 (*n* = 19)	9 (47.3%)	10 (52.7%)	0.583
MDS-isolated 5q- (*n* = 1)	1 (100%)	0 (0%)	0.233

Table 4
The association between chromosomal abnormalities and MDS subgroups.

Primary MDS types	MDS-EB (*n* = 28)	MDS- non EB (*n* = 32)	OR (95% CI)	p
Abnormal karyotype (n)	16	9		
Normal karyotype (n)	12	23	3.407 (1.164–9.976)	0.022
Complex karyotype (≥3 chromosomal abnormality)	12	6	3.25 (1.018–10.379)	0.042
Non- Complex karyotype (<3 chromosomal abnormality)	16	26		

Note: MDS-EB: MDS with excess blast include MDS-EB1 and MDS-EB2, MDS-non EB: MDS without excess blast.

had trisomy 8 alone. Single chromosomal abnormalities were del (5q), -Y. +8 (trisomy 8) and +11 found in 1/60 patients (1.67%) each (Table 2).

Regarding MDS suptypes, the frequency of the abnormal karyotype was lower than the frequency of the normal karyotype in MDS- SLD ($p = 0.044$) (Table 3).

Patients with abnormal karyotype had higher odds of being MDS-EB (MDS with excess blast) compared to those with normal karyotype (OR = 3.407, 95% CI = 1.164 – 9.976). Patients with complex karyotypes had a higher probability of having MDS-EB compared to those without complex karyotype (adjusted with OR = 3.25, 95% CI = 1.018 – 10.379) (Table 4)

4. Discussion

4.1. Chromosome characteristics

Cytogenetic abnormalities were identified in 25/60 patients (41.67%), which was comparable to that described in patients with primary MDS from the studies of A. Rasid in Pakistan (42.3%), O. Pozdnyakova in the USA (45%), Yasser Elnahass with Egyptian patients (46%), R. Chaubey with Indian patients (47.5%), and Detlef Haase in Germany and Austria (49.8%), but much lower than that found in studies of A. Gmidene (51%) with Tunisian patients, L. Li with Chinese patients (67.5%) [2,9,13-17].

Thirty % of our patients had complex cytogenetics which was higher than reports from Yasser Elnahass with Egyptian patients (12%), Dellef Haase in Germany and Austria (14.5%), A. Rasid in Pakistan (15.5%) [2, 9,13],

In our study, although the frequency of del(5q) met in 9 patients accounted for 15%, only 1 patient had isolated 5q- which accounted for 1.67%, this rate was very low compared to other studies such as Detlef Haase with German and Austria patients (61/595 patients with 10.2%), Yasser Elnahass with Egyptien patients (14%), A. Gmidene (13%) with Tunisian patients [2,9,16]. However, Matsuda et al., found that Japan patients had a much lower frequency of del (5q) (3/102 patients) than the German patients group (39/100 patients) [10]. L. Li et al. also showed that the incidence of 5q- syndrome was only 0.3% in Chinese patients with MDS [17]. It seems that the isolated del(5q) ratio in our study is similar to that of the study of Japanese and Chinese patients, the same ethnic groups in East Asia.

In our study, cytogenetic abnormalities related to prognosis such as trisomy 8 alone, loss of Y alone were observed in only 1 patient, which represented 1.67%. Trisomy 8 as a single chromosomal abnormality was detected in only 2% of the study of Yasser Elnahass with Egyptien patients and 3% of the study of A. Gmidene in Tunisian patients, while it was the most common single chromosomal abnormality in the study of A. Rasid in Pakistan and in the study of L. Li with Chinese patients (9.9% and 19.1%) [9,13,16,17]. Loss Y as a single chromosomal abnormality was detected in only one patient in the study of Yasser Elnahass and A. Gmidene, two patients in the study of A. Rasid [9,13,16].

Other important cytogenetic abnormalities, such as monosomy 7, trisomy 13, trisomy 21, del (12p) were all encountered in combination

with complex abnormality in our study.

4.2. The association between chromosomal abnormalities and MDS subgroups according to WHO

In our study, chromosomal abnormalities were observed frequently in MDS-EB (1 and 2). This result is similar to the studies by Yasser Elnahass, O. Pozdnyakova [9,14]. Detlef Haase et al., also showed that high-risk chromosomal abnormalities were more pronounced in MDS with excess blast [2].

Our study also showed that patients with abnormal karyotype had a higher probability of having MDS-EB (MDS with excess blast) (OR= 3.407, 95% CI=1.164 to 9.976). Similarly, patients with complex karyotypes had a higher odds of being MDS-EB (OR= 3.25, 95% CI=1.018 to 10.379). Subgroup classifying as well as risk scoring in patients with MDS are mainly concerned with an increased susceptibility to AML transformation (acute myelogenous leukemia). However, patients with MDS excessive blast are at risk of rapid transformation, which is similar to patients with complex chromosomal abnormalities. It is possible that the appearrance of complex chromosomal abnormalities is a motivator of the occurrence and increase in blast in patients with MDS.

5. Conclusion

In our study, the complex karyotypes ((≥3 chromosomal abnormality) was the most frequent chromosomal abnormality. Furthemore, our study reveals that patients with abnormal karyotype or complex karyotype had higher odds of being MDS with excess blast. The isolated del (5q) ratio is very low compared to Europe and North Africa, but similar to China and Japan as they are the same countries in East Asia.

Informed consent and patient details

The study protocol was approved by the Ethical Committee in Hanoi Medical University. Patient consent was waived by the committee as this study was a retrospective observational study

This study does not include case details or other personal information or images of patients and any other individuals in an Elsevier publication.

Financial disclosure statement

No financial support was received for this study.

Data availability

Data can be obtained from the corresponding author upon request.

Declaration of Competing Interest

The authors declare that have no conflicts of interest.

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