Cytogenetic characteristics in Vietnamese patients diagnosed with primary myelodysplastic syndromes

Minh Phuong Vu a, b, *, Hong Quang Ha b, Cuc Nhung Nguyen b

a Hanoi Medical University, Department of Hematology, 1 Ton That Tung Street, Hanoi, Vietnam
b Bach Mai Hospital, Center for Hematology and Blood Transfusion, 78 Giai Phong Road, Hanoi, Vietnam

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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 (>5 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 subtypes of MDS. Since then, this classification has been updated twice (2008 and 2016). The 2016 WHO classification defined one type of unclassifiable MDS (MDS-UCG) 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)
were analysed using standard procedures. Chromosomes were stained with G bands, and Bone marrow samples were processed after culture (24) following enrolled in our study.

2.1. Patients

Qualitative data have been expressed as frequency and percentage.

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 [12,5,6]. 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 $x^2$ 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 blasts).

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

| 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 0.18                       |
| Min-max 0.178,514                |
| Bone marrow cellularity (n, %)   |
| Hyperecellular marrow 9 (15%)    |
| Normocellular marrow 30 (50%)    |
| Hypoecellular marrow 21 (35%)    |
| Bone marrow Blasts (%)           |
| Mean 9.76                       |
| Min-max 0–18                     |
| MDS subtypes (n, %)              |
| MDS-SLD 9 (15.0%)                |
| MDS-MLD 22 (36.7%)               |
| MDS-EB1 9 (15%)                  |
| MDS-EB2 19 (31.6%)               |
| Karyotype                        |
| Normal 35                        |
| Abnormal 25                      |
| Single chromosomal abnormality 46.67% |
| 2 chromosomal abnormality 3 (5.0%) |
| $\geq$ 3 chromosomal abnormality 18 (30.0%) |
| Risk categories (IPSS-R)         |
| Very low 2 (3.33%)                |
| Low 15 (25%)                     |
| Intermediate 11                  |
| High 12 (20%)                    |
| Very high 20                     |
| (33.33%)                         |

study was a retrospective observational study.

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 Sq-, 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 ($\geq$ 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
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 subtypes, the frequency of the abnormal karyotype was lower than the frequency of the normal karyotype in MDS-SLD (OR = 1.018, 95% CI = 1.164 – 3.25, 95% CI = 1.164 – 3.25) (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 – 10.379). 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%), Detlef 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 Egyptian patients (14%), A. Gmidene (13%) with Tunisian patients [2,9,16], However, Matsuda et al., found that Japanese 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 Egyptian 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...
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 appearance 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. Furthermore, 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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