CLINICAL, CYTOGENETIC AND SURVIVAL CHARACTERISTICS OF MYELODYSPLASTIC SYNDROME PATIENTS WITH POLYCYTHAEMIA

YUJIAO ZHANG[1], ACTON[1], STEVEN[1], SHAD[1], JIAN LIU[1], BEILI CHEN[2,*]
[1]Xinjiang Medical University, Urumqi, PR China - [2]Department of Hematology, Affiliated Hospital of Guilin Medical University, Guilin, PR China

ABSTRACT

Objective: *To analyse the clinical characteristics, cytogenetic characteristics and survival of patients with myelodysplastic syndrome (MDS) and primordial cell increase.*

Methods: *From January 2016 to January 2018, 120 patients with MDS and protocytosis were included in this study. At the same time, 100 patients with MDS and without primordial cell increase were selected for comparison. Patient data were collected for cytogenetic analysis, and the survival rate, median survival time and median progression time were recorded.*

Results: *The characteristics of clinical information were as follows: 89 male patients and 31 female patients, with an average age of (70.03±9.17) years. A total of 78 patients (65%) had combined diseases, while 62 patients (51.67%) had a smoking and drinking history. The main symptoms included dizziness and fatigue with 69 cases (57.5%), while 42.5% exhibited other symptoms. A total of 57 patients (47.5%) had a decrease in the third system, while 40 patients (33.33%) had a decrease in the second system and 23 patients (19.17%) had a simple decrease in the red system. The median of neutrophils, haemoglobin and platelets were 2.08 (0.00-77.63) × 109/L, 70 (10-158) g/L and 56 (9-1494) × 109/L, respectively. The chromosomal abnormalities observed in this study included number abnormality, structure abnormality and number structure abnormality. The proportion of cytogenetic abnormality in MDS patients with increased primordial cells was higher than that in non-MDS patients with increased primordial cells ($P < 0.05$). The high incidence of abnormal karyotypes were +8, 7q-, and -7 at 16.90, 14.08 and 14.08%, respectively. The median follow-up time was 18 months (3–24 months). The survival rate, median survival time and median progression-free time of MDS patients were lower than those of non-MDS patients ($P<0.05$). However, there was no difference between MDS with protocytosis type 1 and MDS with protocytosis type 2 ($P>0.05$).*

Conclusion: *MDS patients with protocytosis possess distinct clinical and cytogenetic characteristics. Their prognosis is relatively poor and their survival situation is not optimistic.*

Keywords: *Myelodysplastic syndrome, protocytosis, clinical characteristics, cytogenetics, survival.*

DOI: 10.19193/0393-6384_2020_6_523

Received *November 30, 2019;* ***Accepted*** *January 20, 2020*

Introduction

Myelodysplastic syndrome (MDS) is characterised by morbid haematopoiesis, ineffective haematopoiesis and high risk of leukaemia transformation. Notably, it has a high incidence in the population, especially in the elderly, and its clinical treatment effect is not ideal[(1)]. According to the World Health Organization (WHO) classification, MDS belongs to the chronic bone marrow malignant disease group. MDS patients with more primitive cells, such as refractory anaemia with more primitive cells, have a very high probability of transforming into leukaemia, thus resulting in difficult treatment with fewer patients achieving remission. Patients with MDS and protocytosis exhibit high heterogeneity and the median survival time is 6 months to 5 years[(2)].

The clinical manifestations of MDS patients with protocytosis are diverse and their cytogenetic differences are large[(3)], which may be the reason for their different survival conditions. The abnormal karyotype of MDS patients with increased primordial cells has a suggestive effect on the severity, change trend and prognosis of patients.

Clinical data and methods

Clinical data

From January 2016 to January 2018, 120 patients with MDS and protocytosis were included in this study. At the same time, 100 patients with MDS and without primordial cell increase were selected for comparison. MDS patients were classified according to the WHO classification in 2016: MDS with single-line morbid haematopoiesis, MDS with multi-line morbid haematopoiesis, MDS with single-line morbid haematopoiesis and annular iron granulocyte, MDS with multi-line morbid haematopoiesis and annular iron granulocyte, MDS with primitive cell increase type 1, MDS with primitive cell increase type 2, MDS with isolated 5q-, MDS without classification. MDS with protocytosis type 1 and MDS with protocytosis type 2 were identified as MDS with protocytosis.

Other types of MDS patients believe that non-MDS is accompanied by primitive cell proliferation. All patients were treated according to the MDS-related treatment plan of our hospital. All patients fully understood the study and informed consent forms were signed by the patients or their clients.

Inclusion and exclusion criteria

Inclusion criteria were in line with the diagnostic criteria[4]:

• Patients diagnosed with MDS with increased primordial cells;

• Patients with complete clinical data;

• Patients with a low probability of loss of follow-up;

• Patients who voluntarily participate in the study.

Exclusion criteria:

• Patients with other morbid haematopoietic diseases such as megaloblastic anaemia;

• Patients with severe infection, organ failure and severe bleeding that cannot be corrected;

• Patients with poor compliance that are unlikely to persist until the end of the study;

• Patients with incomplete data;

• Patients who are unwilling to participate in the study.

Methods

Clinical data collection

Data were collected from patient medical records or directly when patients were admitted to the hospital. Patients were carefully asked about their relevant information.

Cytogenetic analysis

The posterior superior iliac spine was selected as the puncture point for bone marrow collection. The patient would then lay on the bed on their side, legs bent. The posterior superior iliac spine was selected as a marker. Sterilisation was performed, gloves were worn, a sterile hole towel was placed and the patient was anaesthetised at the periosteum. After fixing the skin with the left hand, a puncture needle was inserted vertically into the bone surface.

When a sense of falling was detected, the puncture needle reached the marrow cavity and fixed. The needle core was drawn out and a syringe was connected to draw approximately 5ml of bone marrow into a green anticoagulant tube for cytogenetics analysis. After disinfecting the super clean table, the bone marrow was inoculated into a culture dish for 24 hours and shaken regularly.

When the culture time was complete, colchicamide was added for a final concentration of 0.05ug/ml to block the metaphase. After the culture, the bone marrow cells were collected by centrifugation. A KCl solution at 37 ^{o}C was added to the cells. The ratio of methanol to glacial acetic acid was 3:1. The bone marrow cells were mixed, fixed three times and then made into cell suspension again.

The appropriate amount of cell suspension was dried on slides. The slides were then collected and analysed via R-banding. The slides were stained with 10% Giemsa's solution and observed using an optical microscope. The karyotypes of bone marrow cells were recorded according to the International System of Human Cytogenetics Nomenclature (ISCN 2013). Clonal abnormality standard (5): ≥2 cell chromosomes increase or rearrange; ≥3 cell chromosomes lose.

Survival follow-up

In addition to multiple treatment and admission, the patient was followed up for outpatient re-examination 1-2 weeks after discharge.

Researchers regularly follow up by phone, SMS, WeChat and other contact methods.

Statistical methods

The data were analysed by SPSS 22.0 software. The measurement data were expressed by mean ± standard deviation ($\bar{x}\pm s$), and the comparison between groups was expressed by t-test.

The count data were expressed by rate, and the comparison between groups was expressed by the chi-squared test, and the difference was statistically significant at $P<0.05$.

Results

Clinical characteristics of MDS patients with protocytosis

The clinical information characteristics of the patients were as follows: 89 male patients and 31 female patients. The average age was (70.03±9.17).

A total of 78 patients (65%) had hypertension, coronary heart disease, chronic bronchitis, cerebrovascular disease and diabetes. A total of 62 patients (51.67%) had a history of smoking and drinking.

The main symptoms included dizziness and asthenia with 69 cases (57.5%), while the other clinical symptoms were skin bleeding, gingival bleeding, epistaxis, hepatosplenomegaly and fever (42.5%) (see Table 1 for further details).

Information	Combined disease					Visiting symptoms					
	H	CHD	CB	CD	DM	DF	SB	GB	E	H	F
Cases	22	18	6	7	25	69	17	12	7	6	9
Proportion	18.33%	15%	5%	5.83%	20.83%	57.5%	14.17%	10%	5.83%	5%	7.5%

Table 1: Clinical information characteristics of patients. *H: Hypertension; CHD: Coronary Heart Disease; CB: Chronic Bronchitis; CD: Cerebrovascular Disease; DM: Diabetes Mellitus; DF: Dizziness and Fatigue; SB: Skin Bleeding; GB: Gingival Bleeding; E: Epistaxis; H: Hepatosplenomegaly; F: Fever.*

The characteristics of laboratory examination information are as follows: 57 patients (47.5%) with a decrease of the tertiary system, 40 patients (33.33%) with a decrease of the secondary system and 23 patients (19.17%) with a decrease of the simple red system.

The median of neutrophils, haemoglobin and platelets were 2.08 (0.00-77.63) × 109/L, 70 (10-158) g/L and 56 (9-1494) × 109/L, respectively.

Cytogenetic characteristics of MDS patients with protocytosis

The chromosomal abnormalities found in this study include number abnormality, structure abnormality and number structure abnormality.

The proportion of cytogenetic abnormalities in MDS patients with increased primordial cells was higher than that in non-MDS patients with increased primordial cells (P<0.05).

Specific karyotype changes are presented in Table 2.

Group		MDS with protocytosis	Abnormal ratio (%)	Non-MDS with protocytosis	Abnormal ratio (%)	χ^2	*P*
Karyotype	Abnormal	71	59.17	32	32	16.168	0.001
	Normal	49	40.83	68	68		
Abnormal number	+8	12	16.90	5	15.63		
	-7	10	14.08	7	21.86		
	+9	7	9.86	2	6.25		
	-Y	7	9.86	3	9.38		
Structural abnormality	7q-	10	14.08	6	18.75		
	5q-	7	9.86	3	9.38		
	t (1;7)	8	11.27	4	12.5		
	t (3;7)	6	8.45	1	3.13		
Number structure exception		4	5.63	1	3.13		

Table 2: Cytogenetic characteristics of MDS patients with protocytosis.

Survival of patients with MDS and protocytosis

The median follow-up time was 18 months (3-24 months). The survival rate, median survival time and median progression-free time of MDS patients were lower than those of non-MDS patients (P<0.05). However, there was no difference between MDS with protocytosis type 1 and MDS with protocytosis type 2 (P>0.05).

Table 3 presents the survival of MDS patients with primitive cell increase.

Group	Cases	SR (%)	χ^2	*P*	MS (months)	χ^2	*P*	MP (months)	χ^2	*P*
MDS-P	120	49.17	7.089	0.008	11	8.562	0.006	9	6.251	0.009
N-MDS-P	100	67			20			16		
MDS-PT1	65	47.69	0.123	0.725	13	0.197	0.699	10	1.088	0.494
MDS-PT2	55	50.91			10			8		

Table 3: Survival of MDS patients with protocytosis. *SR: Survival Rate; MS: Median Survival; MP: Median Progression; MDS-P: MDS with protocytosis; N-MDS-P: Non-MDS with protocytosis; MDS-PT1: MDS with protocytosis type 1; MDS-PT2: MDS with protocytosis type 2.*

Group	Cases	Median survival (months)	χ^2	*P*	Median progression (months)	χ^2	*P*
Normal karyotype	49	17	9.576	0.004	11	7.221	0.007
Abnormal karyotype of simple number or structure	67	15			8		
Number structure abnormal karyotype	4	9			5		

Table 4: Survival of MDS patients with different karyotypes.

Discussion

MDS is a special type of disease in the blood system. Its diagnosis and classification are gradually being standardised with ongoing research. In 2016, the WHO formulated nine types of MDS.

Combined with the bone marrow cell morphology and genetic characteristics of MDS, it has a greater reference significance for diagnosis and treatment. MDS is a special type of MDS. In recent years, it has been found that MDS is more common among elderly patients (approximately 80% of cases), and more common in male patients than in female patients[6, 7]. In this study, the investigation of patients also has similar results. Moreover, elderly male patients are more likely to have MDS. Elderly patients with a decline in physical function can be combined with a variety of chronic diseases.

The clinical symptoms of MDS patients with increased primordial cells are mostly anaemia symptoms. The MDS patients with increased primordial cells included in this study experienced dizziness and fatigue when seeking treatment for the initial symptom. Patients' symptoms resulted from the decrease of blood cell lines and the poor constitution of the elderly patients, while other clinical symptoms such as fever also appeared. The laboratory examination also supports the disease characteristics of MDS. The peripheral blood examination shows that the number of single lineages is reduced to three. Conclusions regarding the clinical characteristics of MDS patients with increased primordial cells are that elderly male patients are more common, anaemia is the first symptom and peripheral blood examination shows the decrease of blood cells.

Cytogenetic abnormalities are more common in MDS than in other diseases. It has been reported that there over 2700 types of abnormal changes can occur in MDS[8]. Therefore, the chromosomal heterogeneity of MDS is massive, and different types of MDS have relatively characteristic cytogenetic changes. The chromosome abnormality of cells can be a single change in the number, structure abnormality, or a simultaneous complex change of number and structure abnormality. This change can involve each of the 46 chromosomes. In this study, the abnormal karyotypes with high incidence in 120 MDS patients with protocytosis were +8, 7q- and -7 at 16.90, 14.08 and 14.08%, respectively.

In contrast with foreign studies, which reported that the incidence of chromosomal abnormalities in MDS population is -5/5q-[9, 10], the present study suggests that this variation is relatively rare in MDS patients in China. Wang et al. also suggest that +8 is the most common abnormal type[11, 12]. The occurrence of chromosomal abnormalities in patients with MDS at medium and high risk is more common than that in patients with MDS at low risk, while MDS with an increase of primordial cells belongs to the medium- and high-risk groups, among which complex chromosomal abnormalities are more common. Therefore, it can be inferred that the cytogenetic characteristics of MDS patients with protocytosis include +8, 7q-, -7, and more complex karyotypes than other types of MDS, thus suggesting that the more serious the disease, the more common chromosomal abnormalities with poor prognosis become.

At present, a more unified theory is that cytogenetics is an independent influencing factor of MDS prognosis[13]. Compared to other types of MDS patients, the survival rate, median survival period and median progression period of 120 MDS patients with protocytosis were lower, which is consistent with increasingly complex abnormal chromosome changes. Cytogenetics was analysed as an independent factor in multiple prognostic evaluation systems, such as IPSS[14, 15]. Thus, we can predict the survival of patients according to their karyotype.

In summation, MDS patients with primitive cell increase have distinct clinical and cytogenetic characteristics, their prognosis is relatively poor and their survival situation is not optimistic.

References

1) Shao ZW, Sun WW, Ma N, Yang FR, Zhang K, et al. Exploration and practice of teaching reform of clinical hematology examination course after "five changes and four changes". China Higher Med Educ 2018; 1: 76-77.
2) Hasserjian RP, Kelley TW, Weinberg OK, Morgan EA, Fend F. Genetic Testing in the Diagnosis and Biology of Myeloid Neoplasms (Excluding Acute Leukemias). Am J Clin Pathol 2019; 152: 302-321.
3) Choi SM, Van Norman SB, Bixby DL, Shao L. Cytogenomic array detects a subset of myelodysplastic syndrome with increased risk that is invisible to conventional karyotype. Genes Chromosomes Cancer 2019; 58: 756-774.
4) Zhang Q, Liu L, Liao MY, Tang XQ, Wang L, et al. Differential diagnosis model of hypoproliferative myelodysplastic syndrome and aplastic anemia. Int J Blood Transfus Hematol 2016; 39: 191-199.

5) Zeng Y. Application and modification of methods for chromosome culture, preparation and analysis. Chin J Med Genet 2017; 34: 915-918.
6) An N, Deng YY, Wu LJ. Predictive values of iPAB and STAF scoring systems for paroxysmal atrial fibrillation in patients with acute ischemic stroke. China Med 2019; 14: 357-361.
7) Yang YY, Yang JH, Wang D. Biological Characteristics and Risk Factors for Prognosis of Myelodysplastic Syndrome. J Exp Hematol 2017; 25: 1113-1117.
8) Mitsui T, Yokohama A, Koiso H, Saito A, Toyama K, et al. Prognostic impact of trisomy 21 in follicular lymphoma. Br J Haematol 2019; 184: 570-577.
9) Moreno Berggren D, Folkvaljon Y, Engvall M, Sundberg J, Lambe M, et al. Prognostic scoring systems for myelodysplastic syndromes (MDS) in a population-based setting: a report from the Swedish MDS register. Br J Haematol 2018; 181: 614-627.
10) Nomdedeu M, Calvo X, Pereira A, Carrió A, Solé F, et al. Prognostic impact of chromosomal translocations in myelodysplastic syndromes and chronic myelomonocytic leukemia patients. A study by the spanish group of myelodysplastic syndromes. Genes Chromosomes Cancer 2016; 55: 322-327.
11) Zhao D, Zhang ZH, Li LF, Wang CJ, Wang MY, et al. Cytogenetic analysis of 90 children with myelodysplastic syndrome. Chin J Med Genet 2019; 36: 391-393.
12) Ma JL, Li XL, Zhang P, Xiang LL, Li H, et al. Analysis of the factors influencing the efficacy of desetabine in the treatment of myelodysplastic syndrome. J Chin Physician 2018; 20: 1417-1420.
13) Du LH, Ma J, Jiang YF, Zhao WH, Yao YB. The expression of HIF-1α in myelodysplastic syndrome and its clinical prognostic value. J Guangxi Med Univ 2017; 34: 730-733.
14) Liu JX, Wang HQ. Progress in diagnosis and treatment of myelodysplastic syndrome. Chin J Cancer Control 2017; 9: 158-163.
15) Choi SM, Van Norman SB, Bixby DL, Shao L. Cytogenomic array detects a subset of myelodysplastic syndrome with increased risk that is invisible to conventional karyotype. Genes Chromosomes Cancer 2019; 58: 756-774.

Corresponding Author:
Beili Chen
Email: hqiy06@163.com
(China)