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Original Article

Effect of decitabine and thalidomide on the immunological effect and bone marrow mesenchymal stem cells of patients with myelodysplastic syndrome

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Abstract: Objective: This study intended to investigate the therapeutic effect of decitabine and thalidomide on myelodysplastic syndrome (MDS), immunological effect and effective mesenchymal stem cells (MSCs). Methods: Altogether 62 patients with MDS diagnosed in our hospital were selected. Patients who received 5-day treatment mainly and received decitabine from the 1st day to the 5th day were collected as group A (A), while patients who received thalidomide 1st to 5th day as in group A were collected as group B (B). The immunologic effects, blood and bone marrow index levels, clinical effects and adverse reactions of group A and group B before and after intervention were observed. Results: Th17 in the two groups after intervention were evidently lower than that before intervention, and the decrease of Th17 cells in group B after intervention was more obvious than that in group A ($P<0.001$). Th22 cells in the two groups after intervention were evidently down-regulated compared with those before intervention, and the down-regulation of Th17 cells in group B after intervention was more obvious than that in group A ($P<0.001$). However, compared with group A, the levels of CD3+, CD4+, CD4+/CD8+ in serum of group B increased more obviously and CD8+ decreased more obviously after intervention. The white blood cell count of group B after intervention was evidently higher than that of group A ($P<0.001$). The hemoglobin concentration after intervention in group B was evidently higher than that in group A ($P<0.001$). The platelet count after intervention in group A was evidently higher than that in group B ($P<0.001$). The total effective rate in group B was evidently higher than that in group A ($P<0.05$). Conclusion: The combination of decitabine and thalidomide has a better regulatory role in the immunological mechanism and bone marrow mesenchymal stem cells of patients with MDS than the single decitabine therapy on the premise of ensuring clinical efficacy.

Keywords: Decitabine, thalidomide, myelodysplastic syndrome, curative effect, immunological effect, bone marrow mesenchymal stem cells

Introduction

Myelodysplastic syndrome (MDS) is a heterogeneous disease composed of heterogeneous myeloma [1-3]. The risk of patients developing acute myeloid leukemia is very high due to low hematopoietic efficiency [4]. The incidence of MDS increases greatly with age [5, 6]. The epidemiological evaluation of MDS has been hindered by the continuous development of diagnostic criteria and the classification of MDS as cancer. Poor understanding of patients with early MDS will lead to the lack of timely and effective treatment [7, 8].

Chemotherapy and hematopoietic stem cell transplantation are currently the main clinical treatments for MDS [9, 10]. Decitabine is a hypomethylating agent and can reactivate tumor suppressor genes by demethylating them [11]. In recent years, decitabine has become a common clinical drug for patients with MDS [12]. Decitabine has been mainly applied as monotherapy, but some studies have shown that the combination with various reagents such as vorinostat, thalidomide and decitabine gemtuzumab can effectively improve the prognosis of patients with MDS [13]. Thalidomide is a well-known angiogenesis inhibitor and immunomodulator, which has anti-angiogenic activity, can reduce tumor necrosis factor-α, and can be applied for the treatment of MDS, multiple myeloma and other diseases [14, 15]. The mechanism for promoting the development of

Table 1. General clinical data

Group	Group A (n=32)	Group B (n=30)	X^2	P
Age (years)			0.022	0.881
<59.46	8 (25.00)	8 (26.67)		
>59.46	24 (75.00)	22 (73.33)		
Gender			0.625	0.429
Male	16 (50.00)	12 (40.00)		
Female	16 (50.00)	18 (60.00)		
Hypertension			1.245	0.265
Yes	28 (87.50)	23 (76.67)		
No	4 (12.50)	7 (23.33)		
Diabetes			0.389	0.533
Yes	20 (62.50)	21 (70.00)		
No	12 (37.50)	9 (30.00)		
Diagnostic type			0.453	0.767
Refractory anemia	10 (31.25)	10 (33.33)		
Refractory anemia with ring sideroblast	11 (34.38)	12 (40.00)		
Refractory anemia with increase of primitive cells	11 (34.38)	8 (26.67)		
Risk			0.230	0.632
Moderate risk I	13 (40.63)	14 (46.67)		
Moderate risk II	19 (59.38)	16 (53.33)		
High risk	0 (0.00)	0 (0.00)		

MDS diseases is complex. Relevant studies have shown that the occurrence of MDS is closely related to family genetic disease history, autoimmune effect abnormalities and changes in bone marrow micro-environment [16, 17].

This study aimed to analyze the therapeutic role of decitabine and thalidomide on patients with MDS, immunological effect and bone marrow mesenchymal stem cells through two different therapeutic schemes.

General data and methods

General data

Sixty-two patients with MDS diagnosed in our hospital were selected. Patients who received conventional MDS treatment (mainly with 5 d regimen and decitabine from the 1st day to the 5th day) were collected as group A (A), while patients who received thalidomide on the basis of group A were collected as group B (B). There were 32 cases in group A and 30 cases in group B. Inclusion criteria: (1) Patients were diagnosed as MDS and treated in our hospital, which was referred to the World Health Organization's Diagnostic Criteria for MDS [18]; participants had no abortion caused by chromosome, anatomy, endocrine abnormalities, reproductive system infection and autoimmune diseases. Exclusion criteria: (2) Patients with contraindications to the drugs applied in this study; patients had other primary diseases of morbid hematopoiesis and hematocytopenia; patients with hypertension, AIDS and various blood diseases. Participants and their families signed informed consent forms in advance. The study was approved by the Ethics Committee.

Method

Group A: Patients were mainly treated with 5 d regimen, decitabine (SFDA Approval No. H20130067, Hansoh Pharma Co., Ltd., Jiangsu) was given intravenously from the 1st day to the 5th day, and the intravenous drip was completed within 1 h.

Group B: Patients were given thalidomide on the basis of group A (SFDA Approval No. H32026129, Changzhou Pharmaceutical Factory Co., Ltd.). After continuous oral administration of 50 mg/d thalidomide for 1 week, the dosage was adjusted to 100 mg/d, and the same medication was applied for 1 week.

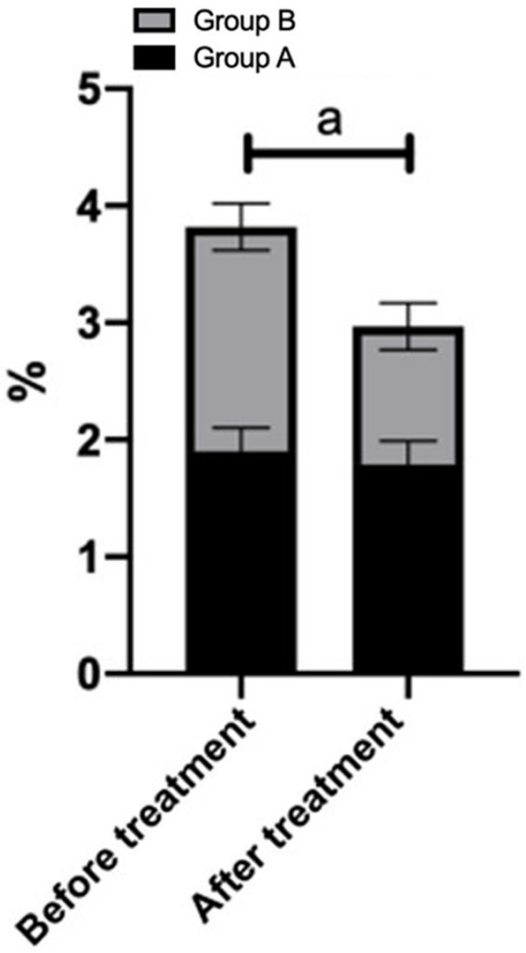

Figure 1. Changes of Th17 cells before and after intervention in group A and group B. There was no evident difference in Th17 cells between group A and group B before intervention (P>0.05). The Th17 cells in the two groups after intervention were evidently lower than before intervention, and the Th17 cells in group B patients after intervention were evidently lower than those in group A patients. Note: a means P<0.001.

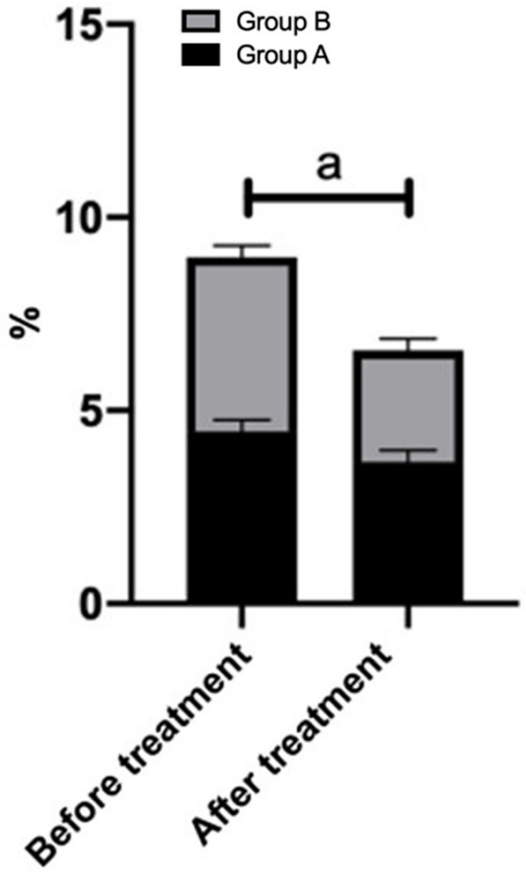

Figure 2. Changes of Th22 cells before and after intervention in group A and group B. There was no evident difference in Th22 cells between group A and group B before intervention (P>0.05). The Th22 cells in the two groups after intervention were evidently lower than before intervention, and the Th22 cells in group B after intervention were evidently lower than those in group A. Note: a means P<0.001.

Outcome measures

Immunological role was analyzed before and after intervention in group A and group B (fasting venous blood of elbow was collected before and after intervention in both groups, and Th17 cells, Th22 cells, CD3+, CD4+, CD8+, CD4+/CD8+ levels were detected by flow cytometry). The blood and bone marrow index levels (including white blood cell count, hemoglobin concentration, platelet count, bone marrow mesenchymal stem cell ratio) of patients in group A and group B before and after intervention were compared. The clinical efficacy of group A and group B was compared [19]. The adverse reactions (including nausea and vomiting, fever, myelosuppression, thermal neutropenia, headache) of group A and group B were compared.

Statistical methods

SPSS 17.0 (Beijing Bi Insight Information Technology Co., Ltd.) was applied for statistical analysis. The counting data were represented by [n (%)] and tested by X^2 test. The measurement data were represented as (x ± s) and tested by independent sample t test. When P< 0.05, the difference was statistically evident.

Result

General clinical data of A and B

There was no evident difference between A and B in general clinical data (P>0.05) (**Table 1**).

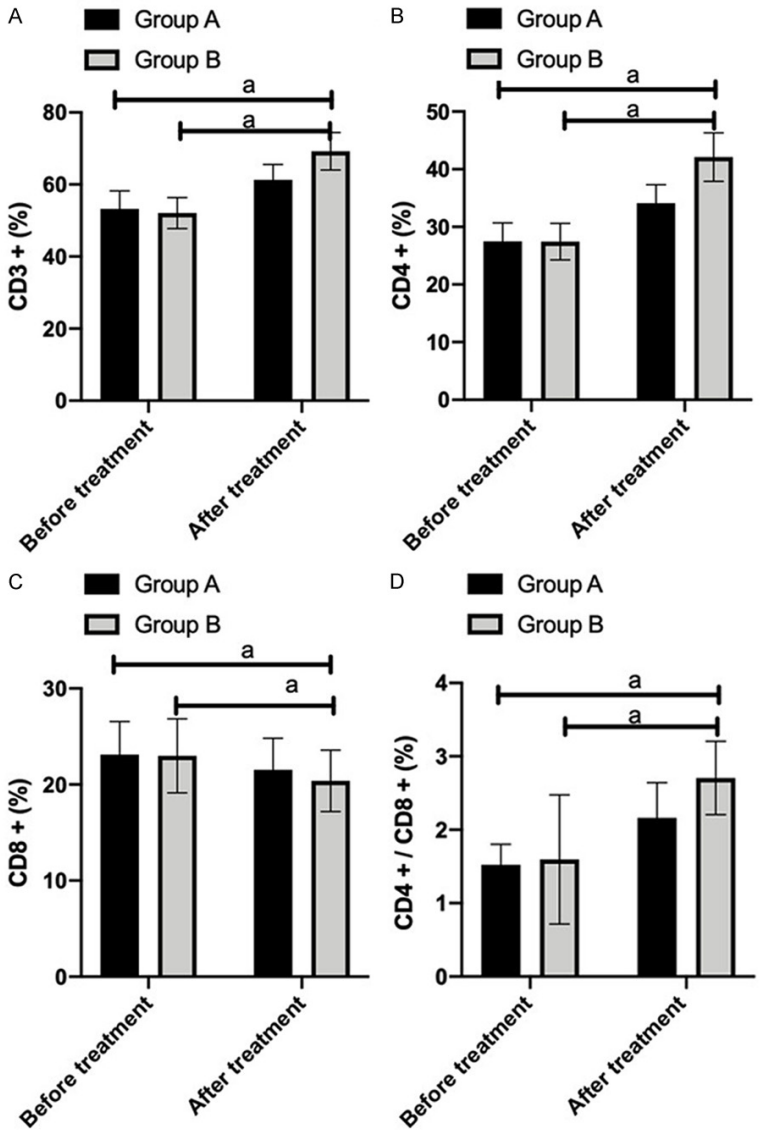

Figure 3. Levels of immune indexes before and after intervention in group A and group B. A. CD3+ (%) level of patients in group A and group B; B. CD4+ (%) level of patients in group A and group B; C. CD8+ (%) level of patients in group A and group B; D. CD4+/CD8+ (%) levels of patients in groups A and B; a means P<0.05.

Analysis of immunological effects before and after intervention in groups A and B

Changes of Th17 cells in groups A and B before and after intervention: The Th17 cells of group A before and after intervention were (1.90 ± 0.20)%, (1.79 ± 0.20)%, while those of group B before and after intervention were (1.92 ± 0.20)%, (1.18 ± 0.20)%. There was no evident difference in Th17 cells between A and B before intervention (P>0.05). Th17 cells in the two groups after intervention were evidently lower than before intervention, and the decrease of Th17 cells in group B after intervention was more obvious than that in group A (P<0.001). See **Figure 1**.

The changes of Th22 cells before and after intervention in group A and group B: The Th22 cells of group A patients before and after intervention were (4.45 ± 0.30)%, (3.67 ± 0.30)%, while the Th17 cells of group B patients before and after intervention were (4.52 ± 0.30)%, (2.89 ± 0.30)%. There was no evident difference in Th22 cells between A and B before intervention (P>0.05). Th22 cells in the two groups after intervention were evidently down-regulated compared with those before intervention, and the down-regulation effect of Th17 cells in group B after intervention was more obvious than that in group A (P< 0.001). See **Figure 2**.

Immune index levels before and after intervention in group A and group B: CD3+, CD4+, CD8+, CD4+/CD8+ in A and B were tested by flow cytometry. The results showed that CD3+, CD4+, CD4+/CD8+ in group A and group B after intervention increased (P<0.05), while CD8+ decreased. However, after intervention, CD3+, CD4+, CD4+/CD8+ in B increased more obviously and CD8+ decreased more obviously compared with A, but the difference was not statistically evident (**Figures 3**, **4**).

Comparison of blood and myelogram indexes before and after intervention between group A and Group B patients

White blood cell count: There was no evident difference in white blood cell count between A and B before intervention (P>0.05). The white blood cell count of A and B after intervention

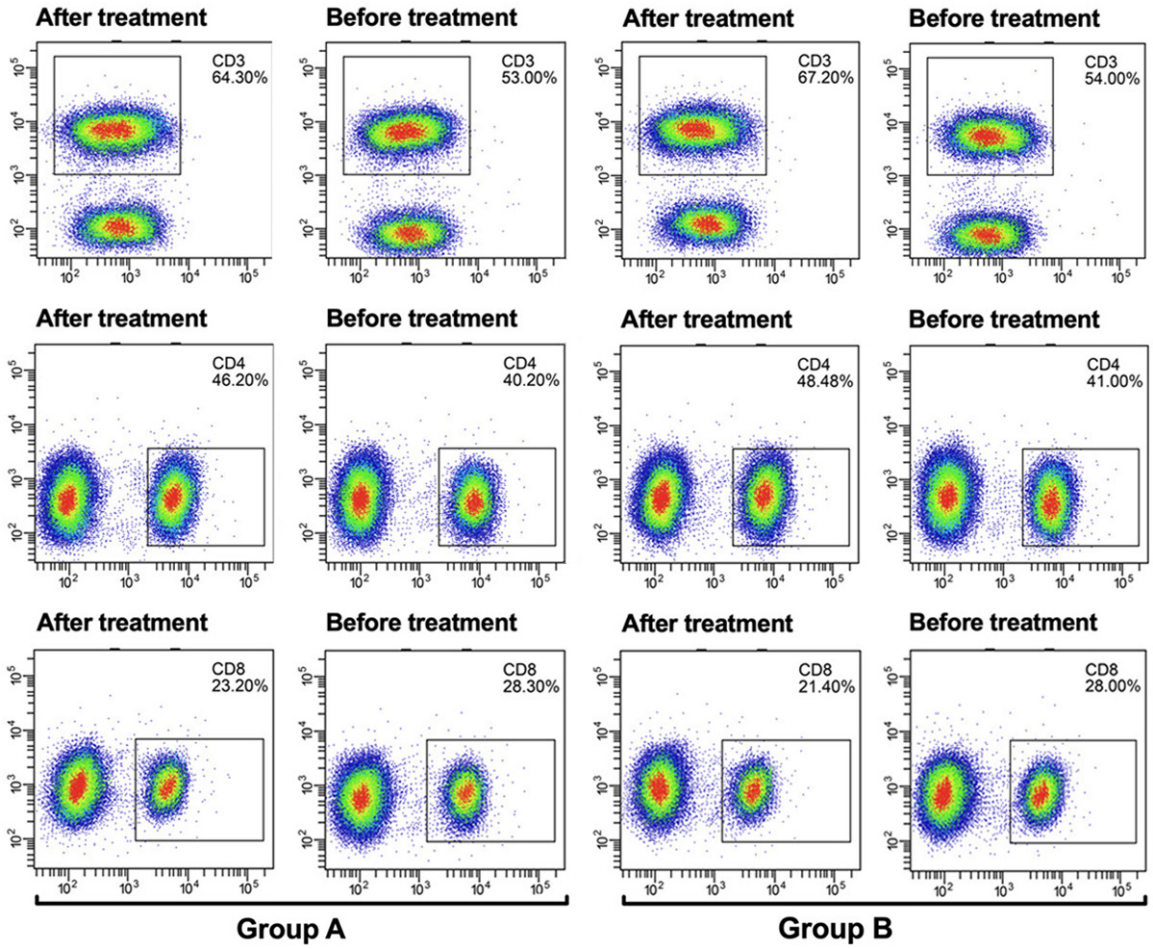

Figure 4. Original figures of flow cytometry.

was evidently higher than that before intervention, and the white blood cell count of group B after intervention was evidently higher than that of group A (P<0.001). See **Figure 5**.

Hemoglobin concentration: There was no evident difference in hemoglobin concentration between A and B before intervention (P>0.05). The hemoglobin concentration after intervention in both groups was evidently higher than that before intervention, and the hemoglobin concentration after intervention in group B was evidently higher than that in group A (P<0.001). See **Figure 6**.

Platelet count: There was no evident difference in platelet count between A and B before intervention (P>0.05). The platelet count after intervention in both groups was evidently higher than that before intervention, and the platelet count after intervention in group A was evidently higher than that in group B (P<0.001). See **Figure 7**.

Proportion of bone marrow mesenchymal stem cells %: There was no evident difference in the proportion of bone marrow mesenchymal stem cells between A and B before intervention (P>0.05). The proportion of bone marrow mesenchymal stem cells after intervention in both groups was evidently lower than that before intervention, and the proportion of bone marrow mesenchymal stem cells after intervention in group B was evidently lower than that in group A (P<0.001). See **Figure 8**.

Analysis of clinical efficacy and adverse reactions of groups A and B

Clinical efficacy: The curative role analysis of A and B showed that the total effective rate of B was evidently higher than that of A (P<0.05). See **Table 2**.

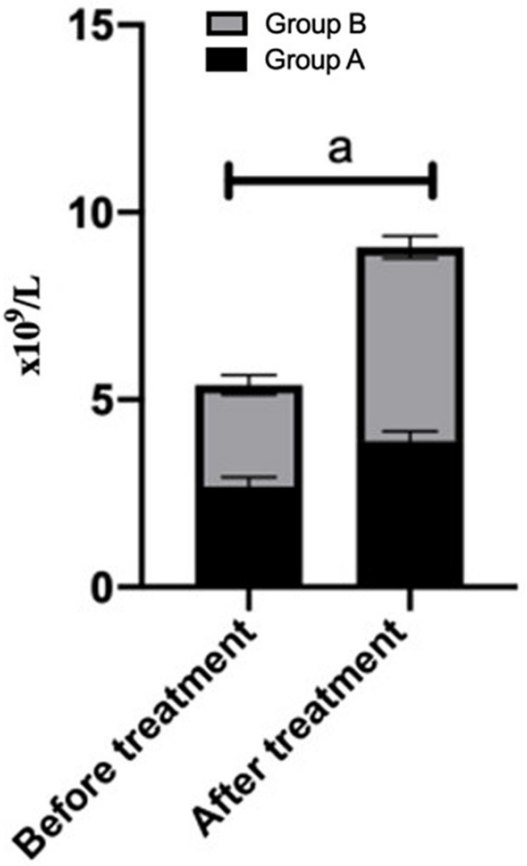

Figure 5. White blood cell count. The white blood cell count of group A and group B after intervention was evidently higher than that before intervention, and the white blood cell count of group B after intervention was evidently higher than that of group A. a means P<0.001.

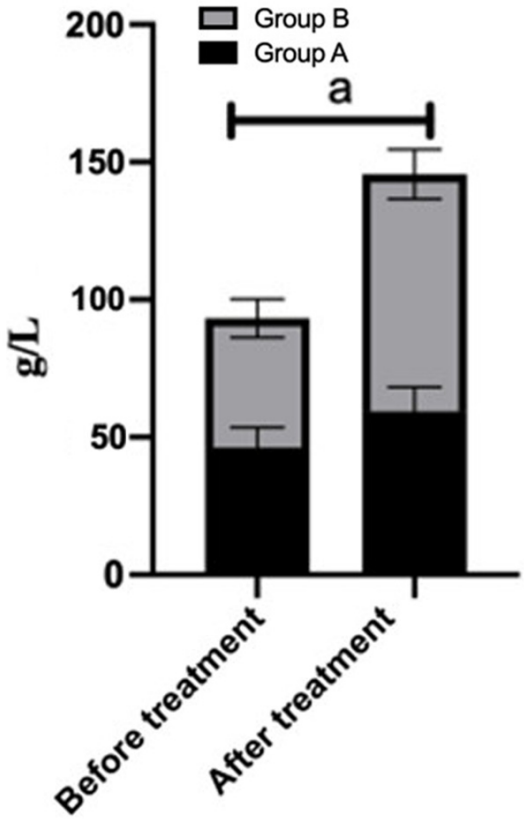

Figure 6. Hemoglobin concentration. The hemoglobin concentration after intervention in both groups was evidently higher than that before intervention, and the hemoglobin concentration after intervention in group B was evidently higher than that in group A. a means P<0.001.

Adverse reactions: The total adverse reaction rate of nausea, vomiting, fever, myelosuppression, thermal neutropenia and headache in A was 28.13%, while that of nausea, vomiting, fever, myelosuppression, thermal neutropenia and headache in B was 23.33%. The incidence of adverse reactions in B was lower than that in A (P>0.05). See **Table 3**.

Discussion

MDS has a rising trend with the deterioration of diseases [20]. Patients with MDS have weakened immune surveillance due to abnormal immune mechanism, thus causing a series of diseased manifestationss [21]. Bone mesenchymal stem cells with immunoregulatory properties are important factors indicating the development of MDS. Clinically, it is very important to find a more safe and effective treatment scheme for relieving the physiological pain and syndromes of patients with MDS [22]. In this study, we analyzed the role of decitabine and thalidomide on the therapeutic efficacy, immunological effects and bone marrow mesenchymal stem cells of patients with MDS.

Clinical data suggested that decitabine had a good effect on promoting the stability of the disease, improving the prognosis of MDS, and prolonging the median time for MDS patients to transform into leukemia and die. However, the single use of decitabine is highly dose-dependent, and the adverse drug effects caused by large doses are also important clinical problems yet to be solved [23]. In this study, through the analysis of immunologic effector cells before and after intervention, we found that Th17 cells after intervention in both

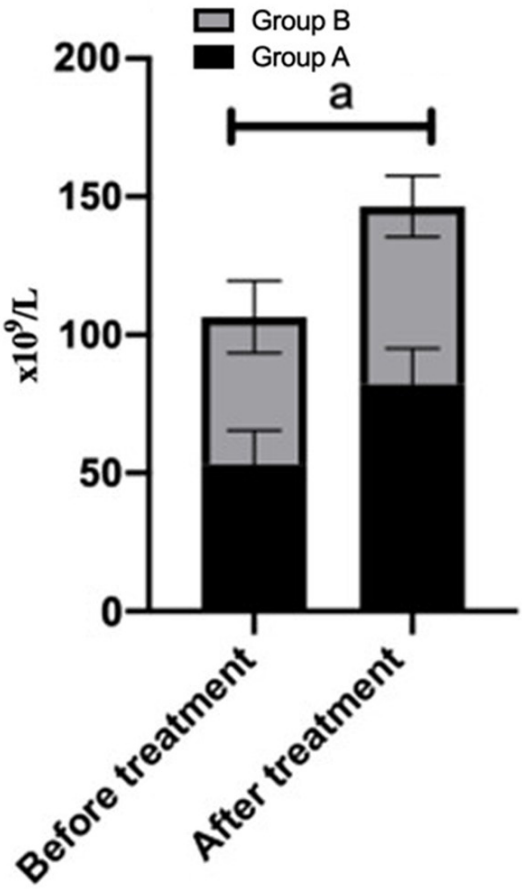

Figure 7. Platelet count. The platelet count after intervention in both groups was evidently higher than that before intervention, and the platelet count after intervention in group A was evidently higher than that in group B (P<0.001). a means P<0.001.

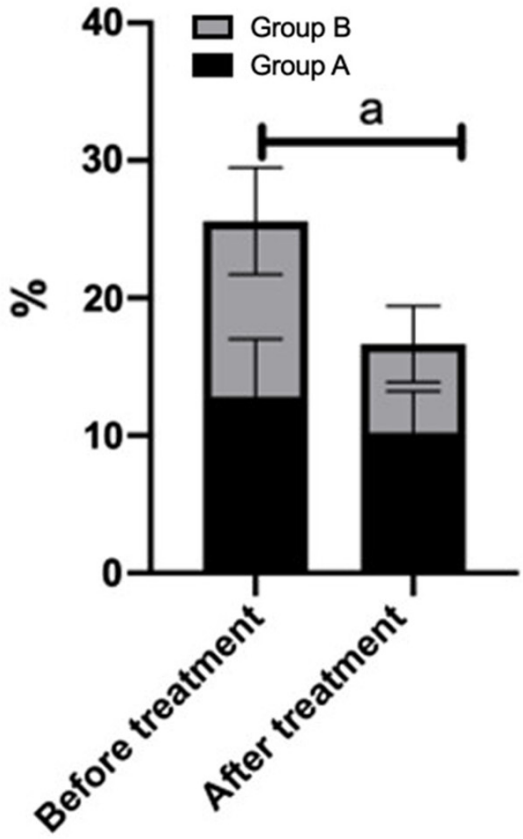

Figure 8. Proportion of bone marrow mesenchymal stem cells. The proportion of bone marrow mesenchymal stem cells after intervention in both groups was evidently lower than that before intervention, and the proportion of bone marrow mesenchymal stem cells after intervention in group B was evidently lower than that in group A. a means P<0.001.

groups were evidently lower than that before intervention, and the down-regulation effect of Th17 and Th22 cells in patients with MDS after intervention with decitabine and thalidomide was evidently higher than that of patients with decitabine alone. Moreover, CD3+, CD4+, CD8+, CD4+/CD8+ measured by flow cytometry showed that those in patients with MDS after intervention with decitabine and thalidomide were increased to a greater extent. It was previously shown that thalidomide could correct immune abnormalities by improving CD3+, CD4+ and CD8+ levels [24]. Therefore, we believed that the combination of decitabine and thalidomide had a better regulatory effect on the immune suppression of patients.

Then, by comparing the blood and bone marrow index levels of group A and group B of patients, we found that the hemoglobin concentration, white blood cell count and platelet count of A and B after intervention were evidently higher than those before intervention. Among them, the hemoglobin concentration and white blood cell count of patients with MDS after intervention with decitabine combined with thalidomide were evidently higher than those of patients with decitabine alone, but the up-regulation of platelet count after intervention was lower than that of patients with decitabine alone. The proportion of bone marrow mesenchymal stem cells after intervention in both groups was evidently lower than that before intervention, and the proportion of bone marrow mesenchymal stem cells after intervention in patients treated with decitabine and thalidomide was evidently lower. MDS is caused by abnormal hematopoietic micro-environment of bone marrow, clonal proliferation of hematopoietic stem cells, and bone marrow mesenchymal stem cells are an

Table 2. The curative role analysis of A and B showed

Group	Group A (n=32)	Group B (n=30)	X^2	P
Complete remission	4 (12.50)	9 (30.00)	-	-
Partial remission	8 (25.00)	8 (26.67)	-	-
Progression	8 (25.00)	9 (30.00)	-	-
Ineffective	12 (37.50)	4 (13.33)	-	-
Total effective rate of treatment	20 (62.50)	26 (86.67)	4.723	0.030

Table 3. Analysis of adverse reactions of A and B

Group	Group A (n=32)	Group B (n=30)	X^2	P
Nausea and vomiting	4 (12.50)	2 (6.67)	-	-
Fever	3 (9.38)	2 (6.67)	-	-
Bone marrow suppression	0 (0.00)	0 (0.00)	-	-
Thermal neutropenia	0 (0.00)	0 (0.00)		
Headache	2 (6.25)	3 (30.00)	-	-
Total adverse reaction rate	9 (28.13)	7 (23.33)	0.186	0.666

important component of hematopoietic microenvironment [25]. A large number of studies have proved that thalidomide can inhibit the abnormal proliferation of bone marrow cells, promote the recovery of hematopoietic function, and improve the body's bone and marrow images [26]. Moreover, Zhao et al. also found that decitabine and thalidomide treatment had better regulatory effect on blood and bone marrow indexes of patients [27]. Finally, at the end of the treatment course, we compared the clinical efficacy and adverse reactions of patients. The results showed that decitabine combined with thalidomide in the treatment of MDS reduced the total adverse reaction rate of nausea, vomiting, fever, myelosuppression, thermal neutropenia and headache to some extent.

In this study, there are still some deficiencies. For example, the data display of other blood indexes of patients still needs to be supplemented, and the time point of experimental design can be more specific. These deficiencies will produce certain errors in the data of this study. In view of the above deficiencies, we will continue to refer to the relevant research results on the treatment of MDS in order to enrich the actual clinical data in the later stage, and regularly follow up the patients to continuously improve the test.

To sum up, the combination of decitabine and thalidomide treatment has better regulatory effect on the immunological mechanism and effective bone marrow mesenchymal stem cells of patients with MDS than single decitabine treatment on the premise of ensuring clinical efficacy.

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Disclosure of conflict of interest

None.

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