CASE REPORT

Myelodysplastic Syndrome Treated by Integrated Chinese and Western Medicine: A Case Report

Wang Jie, MM; Ding Xiaoqing, MD; Chen Haiyan, MD; Guo Ming, MM; Liu Junxia, MM; Li Ling, MM; Liao Jun, MM; Liao Jing, MM

ABSTRACT

Context • Myelodysplastic syndrome (MDS) is a group of highly heterogeneous, malignant clonal diseases derived from hematopoietic stem cells. PD-1 monoclonal antibodies can have a synergistic effect with hypomethylating agents (HMAs), especially for patients with drug resistance to demethylation drugs. TCM in the treatment of MDS can improve hematological indexes, and for some patients, control the proliferation of primitive cells and delay or even block the transformation to leukemia.

Objective • The study intended to examine the therapeutic effects of programmed cell death-1 (PD-1) inhibitors and azacitidine combined with the Yisuifang Thick Decoction in the treatment of MDS with older, high-risk patients.

Design • The research team performed five prospective case studies.

Setting • The study took place at the East Hospital affiliated with Beijing University of Chinese Medicine in Beijing, China.

Participants • Participants were five older, high-risk MDS patients at the hospital who received PD-1 and azacitidine combined with Yisuifang Thick Decoction between April 2020 and June 2021.

Outcome Measures • The research team measured: (1) treatment duration, (2) curative effects, (3) myelosuppression, (4) immune-related adverse reactions, (5) ending outcomes, and (6) progression-free survival (PFS).

Results • The male to female ratio for the five participants was 3:2, and the median age was 69 years, with a range from 62 to 79 years. Four participants had refractory HR-MDS and one had primary MDS. The median treatment duration was 3 months, with a range from 2 to 4 months, and the median progression-free survival (PFS) was 5 months, with a range from 3 to 14 months. All participants achieved a partial response (PR) or a complete remission with incomplete count recovery (CRi) and showed improvement in serological indexes.

Conclusions • Older, high-risk MDS patients generally have poor physical conditions, often accompanied by a poor karyotype prognosis and a poor prognosis for survival. Therefore, the combination of PD-1, azacytidine, and Yisuifang Thick Decoction may be an effective way to treat HR-MDS. (*Altern Ther Health Med.* 2023;29(6):248-253).

Wang Jie, MM, Hematological Department, Beijing University of Chinese Medicine, Beijing, China. **Ding Xiaoqing**, MD, Chief physician; **Chen Haiyan**, MD, Deputy chief physician; **Guo Ming**, MM, Deputy chief physician; **Liu Junxia**, MM, attending physician; **Li Ling**, MM, attending physician; **Liao Jun**, MM, attending physician; **Liao Jing**, MM, attending physician; Blood Department, Dongfang Hospital, Beijing University of Chinese Medicine, Beijing, China.

Corresponding author: Ding Xiaoqing, MD
E-mail: dxiaoqing8690@163.com

INTRODUCTION

Myelodysplastic syndrome (MDS) is a group of highly heterogeneous, malignant clonal diseases derived from hematopoietic stem cells. It's characterized by one or more lines of blood cells with pathological and ineffective, hematopoietic production and a high risk of transformation to acute myeloid leukemia (AML). The pathogenesis of MDS is complex, and immune disorders, gene mutations, epigenetic abnormalities, and bone-marrow microenvironmental disorders all play important roles in the pathogenesis.[1]

The characteristics of the older population with a high incidence of MDS are high heterogeneity and complex disease. The older population with MDS is increasing

worldwide, and the problems of high early mortality, a low remission rate, and a high recurrence rate need to be solved.

Due to the special physiological and pathological characteristics of older patients with MDS, especially older patients of a greater age, with poor Eastern Cooperative Oncology Group (ECOG) scores, and with many underlying diseases, the treatment is more difficult than younger patients.[2]

Currently, the treatments for MDS mainly include demethylation drugs and immunosuppressants as well as allogeneic, hematopoietic, stem-cell transplantation, which can achieve good efficacy and even a cure. However, the treatments have high risks, including toxicity and relatively large side effects, and some patients have poor tolerance and are prone to serious adverse reactions, such as infections and transgraft-related death.[3,4]

Programmed Cell Death-1 (PD-1)

PD-1/ programmed death-ligand 1 (PD-L1) inhibitors, as the most commonly used immunotherapy drugs at present, have significant clinical efficacy in the treatment of a variety of malignant tumors, but at the same time, these inhibitors can lead to autoimmune tolerance imbalance, involving the normal tissues of the human body and triggering a series of inflammatory reactions, known as immune-related adverse reactions.[5-7]

The positive rate of PD-L1 expression in relapsed refractory MDS patients is significantly higher than that in primary MDS patients. The expression of PD-1 is negatively correlated with DNA methylation, and demethylated drugs can induce a high expression of PD-1.[8]

Bewersdorf et al found that treatment with gemcitabine for AML patients can activate the PD-1/PD-L1 signaling pathway, resulting in dose-dependent expressions of PD-1, PD-L1, and PD-L2, which may be one of the main mechanisms causing demethylation drug resistance.[9] Ferrari et al found that tumor-specific, T-cell-mediated upregulation of PD-L1 in myelodysplastic-syndrome cells didn't affect T-cell killing.[10]

PD-1 inhibitors can have a synergistic effect with hypomethylating agents (HMAs), another treatment for MDS, especially for patients with drug resistance to demethylation drugs, and the combination can benefit patients more.[11]

Hypomethylating agents (HMAs)

At present, drugs targeting DNA methylation include azacitidine and decitabine, which can embed into DNA and inhibit DNA methylation transferase (DNMT), all of which can have a significant demethylation effect.

By inhibiting DNA methyltransferase, HMAs regulate abnormal DNA methylation, restore the expression of tumor-suppressor genes, trigger antitumor immune responses, and exert therapeutic effects.[12] HMA and its combinations have significant advantages as induced remission therapies for MDS.

Moskorz et al found that 53 participants with AML, who received treatment with azacitidine combined with a PD-1 monoclonal antibody, had an objective response rate (ORR) of 34% and a rate of complete remission (CR)/ complete remission with incomplete count recovery (Cri) of 21%, and patients who obtained CR/CRi had a lasting response.[13] In that study, the median overall survival (OS) of 35 evaluable participants was 9.3 months, and despite adverse immune reactions, they responded rapidly to hormone therapy.

Yang et al's recent study confirmed that azacitidine combined with a PD-1 monoclonal antibody in the treatment of MDS can obtain better ORR and median OS and the incidence of immune-related adverse reactions was low, making it a safe and effective treatment plan.[14]

Traditional Chinese medicine (TCM)

Dialectical treatment is the main feature and core of TCM theory, and syndrome is a core part of dialectical treatment. It not only reflects the location, nature, and tendency of a disease at a certain stage but also reflects the essence and pathological changes of the disease.

Huangdi Neijing cloud: "Yin Pingyang secret, spirit is to cure"; "When Yang is in the vulva, Yin is in the inner Yang".[15] In that physiological state, Yin and Yang are in a state of constant movement and change, not in a simple state of balance. The relationship between them should be a state of harmony, and if they aren't in harmony, diseases can arise. Therefore, in the process of clinical treatment, it's necessary to adapt to the ups and downs of Yin and Yang, harmonizing them and making the disease heal by itself.[16]

The involvement of TCM in the treatment of MDS can improve hematological indexes, and for some patients, can control the proliferation of primitive cells and delay or even block the transformation to leukemia, thus improving prognoses. Zhou et al found that TCM syndrome types are closely related to such factors as bone marrow at the primitive-cell level, biochemical indexes, growth factors, and prognostic scores.[17] TCM can have a good curative effect in treating MDS. Combined with Western medicine, it can reduce toxicity and side effects, decrease treatment risks, improve treatment tolerance, and improve patients' quality of life.[18]

Wang et al carried out a review of studies performing syndrome differentiation and classification statistics for patients with MDS, and the review found that the basic pathogenesis of MDS, no matter what type it is, is Qi and blood deficiency and blood stasis.[19]

Integrative Treatments

PD-1/PD-L1 inhibitors. These inhibitors can enhance antitumor immunity by stimulating the body's immune function, which is similar to the TCM Fuzheng, which can dispel evil spirits.[20,21] The fundamental pathogenesis of a malignant tumor is Yang deficiency and Yin knot; Yang deficiency prevents the dissolving of the phlegm stasis and poison knot, and stagnation for a long time can become cancerous.[22-24]

The four qi attributes of a PD-1/PD-L1 inhibitor belong to temperature, which can warm and replenish Yang qi in the body, dissipate stagnant Yin and poison, enable sympathetic circulation of Yin and Yang, restore positive qi, and then prevent evil from going out.

Its five taste attributes belong to Gan and Xin. Gan can cultivate and replenish Yang qi in the body, fueling and dispelling evil spirits. Xin can stimulate Yang Qi, warm water and dampness, and make the accumulation disappear, turbidize Yin, promote evil spirits to change to positive ones and improve the circulation of Qi.

By producing what is called nourishing of the source of fire to eliminate the shade, PD-1/PD-L1 inhibitors can warm the body's Yang qi and dissipate stagnation and Yin toxicity, thus promoting treatment of MDS and AML to achieve a good curative effect.[25-27]

HMAs. The regulation of the DNA methylation process is similar to the theory of Yin and Yang self-harmony and disease self-healing in traditional Chinese medicine.[28,29]

Yisuifang Thick Decoction. The decoction usually includes Codonopsis, Poria mushrooms, stir-fried Atractylodes, Sunburn Astragalus, Angelica, Rehmannia, peony, Ligusticum chuanxiong, cuscuta seed, Polygonum multiflorum, wolfberry, deer horn gum, tortoiseshell gum, tangerine peel, Salvia miltiorrhiza, peach kernel, safflower, leeches, and terrapin.

Using the basic principles of supplementing a deficiency, warming the labor, and dispersing the knot, Su Lao originally created the Yisuifang Thick Decoction and added and reduced the Eight Treasure decoction, to enrich the Qi and blood, activate the blood, and tonify the kidney. The composition of Eight Treasure tonic from the Ruizhutang experience formula can replenish Qi and spleen, nourishing and promoting blood. The Reuse Astragalus, with angelica, can supplement angelica's blood-tonifying decoction and help activate the Eight Treasure decoction's blood effect.

Practitioners use the deer horn gum, tortoiseshell gum, codonopsis, and wolfberry for creation of tortoiseshell and deer horn gums, to provide the Yin filling essence, Qi Zhuang Yang. The Polygonum multiflorum and cuscuta seed tonify the liver and kidney and concentrate the blood, replenished but not dry. The Salvia miltiorrhiza, peach kernel, and safflower support Qi and blood circulation to remove blood stasis. The leeches and terrapin break the blood and expel blood stasis; the blood stasis goes away, and the body produces new blood. Tangerine peel regulates qi and invigorates the spleen, drying dampness and eliminating phlegm, so that the whole prescription activates promptly.

Current Study

A comprehensive consideration of patients' ages, general conditions, combined diseases, gene mutations, chromosomes, and other factors can provide a fine diagnostic stratification and individualized treatment, which is the direction of future research and in-depth development.[30] A continuous in-depth exploration of the organic integration of different drugs can bring hope of realizing a longer survival and a higher quality of life for older MDS patients who aren't suitable for intensive chemotherapy.

The current study intended to examine the therapeutic effects of programmed cell death-1 (PD-1) inhibitors and azacitidine combined with the Yisuifang Thick Decoction in the treatment of MDS with older, high-risk patients.

METHODS

Participants

The research team performed five prospective case studies. The study took place at the East Hospital affiliated with Beijing University of Chinese Medicine in Beijing, China. Potential participants were five older, high-risk MDS patients at the hospital who received PD-1 and azacitidine combined with Yisuifang Thick Decoction between April 2020 and June 2021.

Participants voluntarily received treatments with the Yisuifang Thick Decoction combined with Western medicine.

Procedures

Diagnostic process. The Western diagnoses included excess blasts 2 (EB-2), refractory anemia with excess blasts (RAEB-2), and AML. For TCM, the clinical symptoms and tongue and pulse of the five participants all suggested deficiency of qi and blood, and two had toxic stasis block.[31] Therefore, the research team gave participants a Yisuifang Thick Decoction orally after admission.

Auxiliary examination. At baseline, all participants underwent: (1) a stool analysis; (2) a urine analysis; (3) a test of liver function, (4) a test of kidney function, (5) a coagulation analysis, (6) D-dimer analysis; (7) an electrocardiogram; (8) a lung, computerized tomography (CT) examination; (9) a blood analysis, (10) a bone-marrow smear, (11) a gene-mutation analysis, and (12) a chromosome analysis.

Prescription for Yisuifang Thick Decoction. The decoction included: (1) 15 g of Codonopsis, (2) 15 g of Poria mushrooms, (3) 15 g of stir-fried Atractylodes, (4) 30 g of Sunburn Astragalus, (5) 15 g of Angelica, (6) 15 g of Rehmannia, (7) 15 g of peony, (8) 15 g of Ligusticum chuanxiong, (9) 15 g of cuscuta seed, (10) 15 g of Polygonum multiflorum, (11) 15 g of wolfberry, (12) 10 g of deer horn gum, (13) 10 g of tortoiseshell gum, (14) 15 g of tangerine peel, (15) 15 g of Salvia miltiorrhiza, (16) 10 g of peach kernel, (17) 10 g of safflower, (18) 10 g of leeches, and (19) 10 g of terrapin.

Western medications. The research team purchased the azacitidine and the tirelizumab from manufacturer.

Intervention. The research team treated all participants with Integrated Chinese and Western medicine for 30 days.

Outcome measures. The research team measured: (1) treatment duration, (2) curative effects, (3) myelosuppression, (4) immune-related adverse reactions, (5) ending outcomes, and (6) progression-free survival (PFS).

Intervention

Per day, the Integrated Chinese and Western medicine included: (1) 75 mg/m2 of d1-7 azacitidine, (2) 200mg of d8 tirelizumab (PD-1), and (3) Yisuifang Thick Decoction.

Table 1. MDS Participants' Demographic and Clinical Characteristics at Baseline. The EOCG scores can range from 2 to 3. The IPSS-R scores can range from 5.5 to 9, and 5.5 = high risk, 9 = very high risk.

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5
Age, y	69	62	69	68	79
Gender	Male	Male	Female	Female	Male
EOCG	2	2	3	3	3
Complications	• Hypothyroidism • Hepatitis E	• Hypertension • Diabetes	• Hypertension • Diabetes	• After heart-stent implantation	• Coronary heart disease • Hypertension • Diabetes
TCM diagnosis	Marrow consumption	Marrow consumption	Marrow consumption	Marrow consumption	Marrow consumption
TCM dialectics	Syndrome: • Qi and blood deficiency • Poison stasis block	Syndrome: • Qi and blood deficiency	Syndrome: • Qi and blood deficiency • Poison stasis block	Syndrome: • Qi and blood deficiency	Syndrome: • Qi and blood deficiency
Diagnosis	MDS-RAEB-2	MDS-EB-2	MDS-RAEB-2	MDS-AML	MDS-RAEB-2
MDS risk (IPSS-R)	Very high risk, 9 points	high risk, 5.5 points	Very high risk, 9 points	Very high risk, 9 points	Very high risk, 9 points

Abbreviations: AML, acute myeloid leukemia; EOCG, Eastern Cooperative Oncology Group; EB, excess blasts; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; RAEB, refractory anemia with excess blasts; TCM, Traditional Chinese Medicine

Outcome Measures

Treatment Duration. The research team identified the number of months that each participant received treatment.

Curative effects. The research team identified the types of effects, which included complete remission with incomplete count recovery (Cri) and partial response (PR).

Immune-related adverse reactions. The main cause of adverse immune reactions is immune-drug toxicity. The main pathogenesis is wind pathogen, mixed dampness and heat toxicity, and the clinical manifestations are pruritus, rash, diarrhea, fatigue, and anemia.

PFS. The research team identified the number of months of survival.

RESULTS

Participants

For the five participants, the male to female ratio was 3:2; the median age was 69 years, with a range from 62 to 79 years; and the EOCG levels at admission were 2 and 3 (Table 1). Three participants had refractory anemia with excess blasts (MDS-RAEB-2); one was receiving initial treatment for MDS with excess blasts (MDS-EB-2), and one had MDS-AML. All five participants were transfusion-dependent before treatment. Participants had multiple chronic diseases.

Among the five participants, the four with refractory MDS had poor physiological and pathological conditions, which limited the possibility of intense chemotherapy.

General symptoms such as fatigue and palpitations improved after the oral administration of Yisuifang Thick Decoction upon admission. On that basis, participants received the combined treatment of PD-1 monoclonal antibody and azacitidine at the same time.

Auxiliary Examination

The research team found no obvious abnormalities in participants' stool analyses, urine analyses, tests of liver function, tests of kidney function, coagulation analyses, D-dimer analyses, electrocardiograms, or lung CT examinations. Table 2 shows the results of the blood analyses, bone-marrow smears, gene-mutation analyses, and chromosome analyses.

Table 2. MDS Participants' Auxiliary Examination Results at Baseline.

Index	Case 1	Case 2	Case 3	Case 4	Case 5
Hb, g/L	60	68	76	73	69
WBC, K/ μl	1.15×10^9	3.02×10^9	1.68×10^9	1.26×10^9	1.71×10^9
NEUT, cells/μl	0.32×10^9	0.98×10^9	0.72×10^9	0.26×10^9	1.08×10^9
PLT, platelets/μl	4×10^9	12×10^9	116×10^9	4×10^9	74×10^9
Degree of myelodysplasia	III-IV	II	IV	IV	III
Original granulocyte ratio, %	19	12	14	26	8
Gene mutation	• TET2 • RUNX1 • BCOR • CSF3R • PRPF8 • IKZF1 • PHF6	• DNMT3A • RUNX1 • WT1 • SF3B1	• ASXL1	• ASXL1 • PTPNI1 • KRAS	• TP53 • SF3B1

Abbreviations: ASXL1, additional sex combs like-1; BCOR, B-cell lymphoma corepressor; CSF3R, colony stimulating factor 3 receptor; DNMT3A, DNA methyltransferase 3 alpha; Hb, hemoglobin; IKZF, Ikaros family zinc finger protein 1; KRAS, Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; NEUT, neutrophilic granulocyte; PHF6, plant homeodomain finger 6; PLT, platelet; PRPF8, pre-MRNA processing factor 8; PTPNI1, protein tyrosine phosphatase 1; RUNX1, runt-related transcription factor 1; SF3B1, splicing factor 3B subunit 1; TET2, tet methylcytosine dioxygenase 2; TP53, tumor protein p53; WBC, white blood cell; WT1, Wilms' tumor 1

Table 3. MDS Participants' Adverse Reactions and Outcomes Postintervention.

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5
Treatment status	Recurrent refractory	Initial treatment	Recurrent refractory	Recurrent refractory	Recurrent refractory
Total course of treatment, mos	4	4	3	2	3
Curative effect	PR	CRi	CRi	PR	PR
Myelosuppression	IV	III	IV	IV	III
Immune-related adverse reactions	No	No	Immune pneumonia	No	No
Ending outcome	AML	survival	survival	survival	survival
PFS, mos	5	14	5	3	4

Abbreviations: AML, acute myeloid leukemia; Cri, complete remission with incomplete count recovery; PFS, progression-free survival; PR, partial response

Case 1. The participant had refractory MDS with a complex chromosome karyotype and a lesion of an undetermined space occupying the middle lobe of the right lung.

Case 2. The participant was newly treated for MDS, and a gene test indicated a DNA methyltransferase 3 alpha (DNMT3A) mutation.

Case 3. The participant had refractory MDS and a complex chromosome karyotype, and the gene test indicated an additional sex combs like-1 (ASXL1) mutation.

Case 4. The participant had MDS-AML and a complex chromosome karyotype, and gene detection indicated an ASXL1 mutation.

Case 5. The participant had refractory MDS and a complex chromosome karyotype, and the gene test indicated a tumor protein p53 (TP53) mutation.

Follow-up and Prognosis

Table 3 shows participants' adverse reactions and outcomes. The median treatment duration was 3 months, with a range from 2 to 4 months, and the median progression-free survival (PFS) was 5 months, with a range from 3 to 14 months.

Two participants achieved CRi, and three participants achieved PR. The hematological indexes improved, and the interval between transfusions was prolonged in the transfusion-dependent participants.

The research team regarded the occurrence of dermatitis and immune pneumonia after the third course of treatment for Case 3 as being an immune-related adverse reactions, and symptomatic treatment with hormones and traditional Chinese medicine relieved the symptoms.

DISCUSSION

To meet the needs of patients of all ages, comprehensive treatment of the disease requires more use of TCM. In this regard, the current research team believes that the advantages of TCM syndrome differentiation should receive full play. Researchers should carefully analyze the main contradictions that patients face, so that older patients can receive treatment under the conditions that allow their poor physiological and pathological conditions to improve.

The current study found that PD-1 monoclonal antibodies can have a synergistic effect with azacytidine combined with TCM. The combination of traditional Chinese and Western medicine provides a new diagnostic and treatment plan for older MDS patients with poor physiological conditions.

Immunotherapy is the development direction for the tumor therapy of the future, and TCM is promising in the alleviation of immune-related adverse reactions.

The current study had some limitations. The sample size was small, and data on the immune-related adverse reactions are insufficient. The field still needs a large sample of clinical cases treated with traditional Chinese medicine.

CONCLUSIONS

Older, high-risk MDS patients generally have poor physical conditions, often accompanied by a poor karyotype prognosis and a poor prognosis for survival. Therefore, the combination of PD-1, azacytidine, and Yisuifang Thick Decoction may be an effective way to treat HR-MDS.

DATA AVAILABILITY

The data used to support this study are available from the corresponding author upon request.

AUTHORS' DISCLOSURE STATEMENT

The authors declare that they have no conflicts of interest related to the study.

REFERENCE

1. Nagata Y, Maciejewski JP. The functional mechanisms of mutations in myelodysplastic syndrome. *Leukemia*. 2019;33(12):2779-2794. doi:10.1038/s41375-019-0617-3
2. Graf JR, Forster S, Bruehl FK, et al. Diagnostic and Prognostic Implications of Caspase-1 and PD-L1 Co-Expression Patterns in Myelodysplastic Syndromes. *Cancers (Basel)*. 2021;13(22):5712. doi:10.3390/cancers13225712
3. Fenaux P, Platzbecker U, Ades L. How we manage adults with myelodysplastic syndrome. *Br J Haematol*. 2020;189(6):1016-1027. doi:10.1111/bjh.16206
4. Lee P, Yim R, Yung Y, Chu HT, Yip PK, Gill H. Molecular Targeted Therapy and Immunotherapy for Myelodysplastic Syndrome. *Int J Mol Sci*. 2021;22(19):10232. doi:10.3390/ijms221910232
5. Zhang Z, Chang CK, He Q, et al. Increased PD-1/STAT1 ratio may account for the survival benefit in decitabine therapy for lower risk myelodysplastic syndrome. *Leuk Lymphoma*. 2017;58(4):969-978. doi:10.1080/10428194.2016.1219903
6. Yoyen-Ermis D, Tunali G, Tavukcuoglu E, et al. Myeloid maturation potentiates STAT3-mediated atypical IFN-γ signaling and upregulation of PD-1 ligands in AML and MDS. *Sci Rep*. 2019;9(1):11697. doi:10.1038/s41598-019-48256-4
7. Masarova L, Kantarjian H, Ravandi F, Sharma P, Garcia-Manero G, Daver N. Update on Immunotherapy in AML and MDS: Monoclonal Antibodies and Checkpoint Inhibitors Paving the Road for Clinical Practice. *Adv Exp Med Biol*. 2018;995:97-116. doi:10.1007/978-3-030-02505-2_4
8. Yang H, Bueso-Ramos C, DiNardo C, et al. Expression of PD-L1, PD-L2, PD-1 and CTLA4 in myelodysplastic syndromes is enhanced by treatment with hypomethylating agents. *Leukemia*. 2014;28(6):1280-1288. doi:10.1038/leu.2013.355
9. Bewersdorf JP, Shallis RM, Zeidan AM. Immune checkpoint inhibition in myeloid malignancies: Moving beyond the PD-1/PD-L1 and CTLA-4 pathways. *Blood Rev*. 2021;45:100709. doi:10.1016/j.blre.2020.100709.
10. Ferrari V, Tarke A, Fields H, Tanaka TN, Searles S, Zanetti M. Tumor-specific T cell-mediated upregulation of PD-L1 in myelodysplastic syndrome cells does not affect T-cell killing. *Front Oncol*. 2022;12:915629. doi:10.3389/fonc.2022.915629
11. Geng S, Xu R, Huang X, et al. Dynamics of PD-1 expression are associated with treatment efficacy and prognosis in patients with intermediate/high-risk myelodysplastic syndromes under hypomethylating treatment. *Front Immunol*. 2022;13:950134. doi:10.3389/fimmu.2022.950134

12. Cheng P, Eksioglu EA, Chen X, et al. S100A9-induced overexpression of PD-1/PD-L1 contributes to ineffective hematopoiesis in myelodysplastic syndromes. *Leukemia*. 2019;33(8):2034-2046. doi:10.1038/s41375-019-0397-9
13. Moskorz W, Cosmovici C, Jäger PS, et al. Myelodysplastic syndrome patients display alterations in their immune status reflected by increased PD-L1-expressing stem cells and highly dynamic exhausted T-cell frequencies. *Br J Haematol*. 2021; 1 93(5):941-945. doi:10.1111/bjh.17461.
14. Yang X, Ma L, Zhang X, Huang L, Wei J. Targeting PD-1/PD-L1 pathway in myelodysplastic syndromes and acute myeloid leukemia. *Exp Hematol Oncol*. 2022;11(1):11. doi:10.1186/s40164-022-00263-4
15. Zheng Q, Xu H, Song L, et al. Integrated traditional Chinese and conventional medicine in the treatment of anemia due to lower-risk myelodysplastic syndrome: study protocol for a randomized placebo-controlled trial. *Trials*. 2021;22(1):712. doi:10.1186/s13063-021-05646-2
16. Zhou QB, Zhu QZ, Wang HZ, et al. Traditional Chinese Medicine Containing Arsenic Treated MDS Patients Effectively through Regulating Aberrant Hypomethylation. *Evid Based Complement Alternat Med*. 2020;2020:7469809. doi:10.1155/2020/7469809
17. Zhou QB, Du Y, Zhang SS, Liu ZT, Ma R, Xu YG. Clinical Response to Traditional Chinese Herbs Containing Realgar (As_2S_2) is Related to DNA Methylation Patterns in Bone Marrow DNA from Patients with Myelodysplastic Syndrome with Multilineage Dysplasia. *Cancer Manag Res*. 2021;13:55-63. doi:10.2147/CMAR.S280886
18. Peng X, Zhu X, Di T, et al. The yin-yang of immunity: immune dysregulation in myelodysplastic syndrome with different risk stratification. *Front Immunol*. 2022;13:994053. doi:10.3389/fimmu.2022.994053
19. Wang L, Wu F, Hong Y, Shen L, Zhao L, Lin X. Research progress in the treatment of slow transit constipation by traditional Chinese medicine. [J]. *J Ethnopharmacol*. 2022;290:115075. doi:10.1016/j.jep.2022.115075
20. Shuzhen S, Rou M, Xiaomei H, et al. Karyotype and DNA-Methylation Responses in Myelodysplastic Syndromes following Treatment with Traditional Chinese Formula Containing Arsenic. *Evid Based Complement Alternat Med*. 2012;2012:969476. doi:10.1155/2012/969476
21. Fan T, Feng X, Yokota A, et al. Arsenic Dispensing Powder Promotes Erythropoiesis in Myelodysplastic Syndromes via Downregulation of HIF1A and Upregulation of GATA Factors. *Am J Chin Med*. 2021;49(2):461-485. doi:10.1142/S0192415X2150021X
22. Ma R. Treatment of bone marrow failure syndrome with integrated traditional and Western medicine. *Chin J Integr Med*. 2007;13(2):85-88. doi:10.1007/s11655-007-0085-x
23. Xu M, Ren JY, Guo YC, et al. Effects of arsenic disulfide on apoptosis, histone acetylation, toll like receptor 2 activation, and erythropoiesis in bone marrow mononuclear cells of myelodysplastic syndromes patients in vitro. *Leuk Res*. 2017;62:4-11. doi:10.1016/j.leukres.2017.09.010
24. Han Z, Song L, Qi K, Ding Y, Wei M, Jia Y. Deciphering the Key Pharmacological Pathways and Targets of Yisui Qinghuang Powder That Acts on Myelodysplastic Syndromes Using a Network Pharmacology-Based Strategy. *Evid Based Complement Alternat Med*. 2020;2020:8877295. doi:10.1155/2020/8877295
25. Lv L, Lin G, Gao X, et al. Case-control study of risk factors of myelodysplastic syndromes according to World Health Organization classification in a Chinese population. *Am J Hematol*. 2011;86(2):163-169. doi:10.1002/ajh.21941
26. Efficace F, Cottone F, Abel G, et al. Patient-reported outcomes enhance the survival prediction of traditional disease risk classifications: an international study in patients with myelodysplastic syndromes. *Cancer*. 2018;124(6):1251-1259. doi:10.1002/cncr.31193
27. Haroun F, Solola SA, Nassereddine S, Tabbara I. PD-1 signaling and inhibition in AML and MDS. *Ann Hematol*. 2017;96(9):1441-1448. doi:10.1007/s00277-017-3051-5
28. Jiang J, Wang B, Li J, et al. Total coumarins of Hedyotis diffusa induces apoptosis of myelodysplastic syndrome SKM-1 cells by activation of caspases and inhibition of PI3K/Akt pathway proteins. *J Ethnopharmacol*. 2017;196:253-260. doi:10.1016/j.jep.2016.12.012
29. Linn YC, Lu J, Lim LC, et al. Traditional Chinese herbal medicine in the supportive management of patients with chronic cytopaenic marrow diseases -- a phase I/II clinical study. *Complement Ther Clin Pract*. 2011; 17(3):152-6. doi: 10.1016/j.ctcp. 2011.01.004.
30. Li W, Wang F, Guo R, Bian Z, Song Y. Targeting macrophages in hematological malignancies: recent advances and future directions. *J Hematol Oncol*. 2022;15(1):110. doi:10.1186/s13045-022-01328-x
31. Gao L, Cao M, Li J-Q, Qin XM, Fang J. Traditional Chinese Medicine Network Pharmacology in Cardiovascular Precision Medicine. [J]. *Curr Pharm Des*. 2021;27(26):2925-2933. doi:10.2174/1873428 6MTExhNDUh4