

# The therapeutic effect of modified Huangqi Guizhi Wuwu Tang for multiple myeloma

## An 18-year follow-up case report

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### Abstract

**Rationale:** Multiple myeloma (MM) is a hematologic malignancy characterized by proliferation of clonal plasma cells in the bone marrow. The median survival has increased to 6 years in recent years. But MM remains incurable. Some studies about the effects of Chinese herb medicine on MM have been carried out. Long survival in MM patients through Traditional Chinese Medicine (TCM) therapies has been reported rarely before.

**Patient concerns:** We report a case of a female patient who was diagnosed with MM in 2000 at the age of 49. She received 9 cycles of multiple chemotherapeutic regimens mainly based on melphalan from September 2000 to May 2001. Though her condition was under control in some degree, she discontinued treatment due to significant side effects such as fatigue, hyperhidrosis, fever, chill, larynx mucosa ulcers, pharynx mucosa ulcers, and poor appetite. Instead, she sought treatment with TCM alone.

**Diagnoses:** Based on the TCM theory, the patient's condition was categorized as Xue Bi.

**Interventions:** Up to the present, the patient has been using modified Huangqi Guizhi Wuwu Tang (HGWT) continuously for 18 years. In this prescription, Radix Astragali is an important herb. When the patient's condition worsened, its dosage was increased from 30 to 120g. Besides, she has been eating Radix Astragali porridge or drinking Radix Astragali tea for almost 18 years at the same time.

**Outcomes:** Throughout the period, no obvious side effects have been observed and her health condition remains stable.

**Lessons:** Polysaccharides isolated from *Astragalus membranaceus* (Radix Astragali) and *Polyporus umbellatus* could promote maturation of dendritic cells. Polysaccharides and flavonoids isolated from *Astragalus membranaceus* could regulate bone marrow microenvironment by inhibiting secretion of interleukin (IL)-6, IL-12 p40 and bidirectionally regulating the osteogenic capacity of osteoblasts. Besides, Rhizoma *Atractylodis Macrocephalae*, another important component of the prescription, has inhibitory effects on osteolytic bone lesions. This case suggests TCM treatment may have a positive therapeutic effect on MM. Modified HGWT, especially the Chinese herb medicine Radix Astragali could potentially be an alternative option for the treatment of MM. Both pharmacological studies and randomized clinical trials are needed in the future.

**Abbreviations:** BUN = blood urea nitrogen, HGWT = Huangqi Guizhi Wuwu Tang, Ig = immunoglobulin, IL = interleukin, MM = multiple myeloma, RANKL = receptor activator of NF- $\kappa$ B ligand, TCM = Traditional Chinese Medicine, TLR = toll-like receptor, TNF = tumor necrosis factor.

**Keywords:** modified Huangqi Guizhi Wuwu Tang, multiple myeloma, Radix Astragali

### 1. Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by uncontrolled proliferation of clonal plasma cells in the bone marrow and together with the secretion of monoclonal

immunoglobulins that are detectable in the serum or urine.<sup>[1]</sup> MM accounts for 1.8% of all new cancer cases.<sup>[2]</sup> Over the past decades, because of the availability of novel drugs and new combinations of therapies, toxicity has been markedly reduced. The rate of complete remission, time to progression, progression-free survival, overall survival, and patients' quality of life get obviously improve.<sup>[3]</sup> In the United States, the rate of 5-year relative survival had improved from 26.3% (1975) to 52.7% (2009).<sup>[2]</sup> Unfortunately, MM remains incurable. Side-effects, such as fatigue, anemia, nausea, thrombocytopenia, peripheral neuropathy, neutropenia, venous thromboembolism, the risk of secondary cancers and high costs are the main problems that need to be considered when treatment decisions are made.<sup>[4–8]</sup> In this report, we present a patient with MM who withdrew from therapy of western medicine because of serious side effects. Instead, she chose to receive Traditional Chinese Medicine (TCM) treatment alone and the disease has remained stable so far for 18 years. This case study illustrates modified Huangqi Guizhi Wuwu Tang (HGWT), especially Radix Astragali, could potentially be beneficial for relieving the side effects of chemotherapy, improving living quality, reducing the cost, and achieving a long survival. To our knowledge, some studies about

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the effects of Radix Astragali on MM have been carried out. But clinical case report related this is rare. And long survival in MM patients through TCM therapies has been reported rarely before.

### 1.1. Ethical approval

We have consulted the local Medical Ethics Committee about the ethical approval. This case report does not involve ethical experimentation. It is a past fact. So this case report does not belong to their scope of review. Ethical approval is not necessary.

### 1.2. Patient consent

Written informed consent was obtained from the patient before and after all procedures.

## 2. Case report

### 2.1. Patient information and clinical findings

The patient, a 49-year-old female, was admitted to Nanjing Drum Tower hospital on July 17, 2000, with a history of intermittent dull pain on the left side of waist for more than 30 years, which aggravated 2 months ago. Laboratory tests showed hemoglobin of 76 g/L, serum total protein of 100.8 g/L, serum albumin of 35.1 g/L, serum globulin of 65.7 g/L, serum creatinine of 106.9  $\mu$ mol/L, blood urea nitrogen (BUN) of 6.9 mmol/L, uric acid of 519.5  $\mu$ mol/L, serum immunoglobulin (Ig)G of more than 30 g/L, IgA of 1.31 g/L, IgM of 0.3 g/L. Serum protein electrophoresis showed 37.7% albumin, 3.4%  $\alpha$ 1-globulin, 4.8%  $\alpha$ 2-globulin, 9.4%  $\beta$ -globulin, 44.8%  $\gamma$ -globulin. Emission computed tomography revealed the patient's left renal function was low, and she had hydronephrosis in the right kidney. Glomerular filtration rates of the left and right kidney were 20.27 mL/minute, 63.24 mL/minute, respectively. Single-photon emission computed tomography revealed no obvious abnormality in whole body bone scan. B-scan ultrasonography showed hydronephrosis and kidney stones on the left side, hepatic cyst, cholecystitis, and gallstones. Urinalysis indicated urinary tract infection, albuminuria, and urine occult blood. Bone marrow aspiration and biopsy demonstrated granulocytic series, erythrocyte series, and megakaryocyte were proliferous and active. Plasma cells constituted 10% of bone marrow cells. In focal area, more than 5 plasma cells could be seen in one high power field. Hyperplasia of fibrous tissue could be found in focal area. Serum immunofixation electrophoresis showed the presence of M-protein of the IgG-k type. Based on the National Comprehensive Cancer Network Guidelines,<sup>[9]</sup> the patient was diagnosed with IgG-k type MM. The patient had received melphalan-based therapy from September 2000 to May 2001. After the ninth cycle, her condition was under control to a certain extent. The laboratory tests showed hemoglobin of 101 g/L, serum total protein of 73 g/L, serum albumin of 37 g/L, serum globulin of 36 g/L, creatinine of 60.3  $\mu$ mol/L, BUN of 5.8 mmol/L, IgG of 21 g/L. Serum protein electrophoresis showed 50.6% albumin, 3.3%  $\alpha$ 1-globulin, 6.6%  $\alpha$ 2-globulin, 11.4%  $\beta$ -globulin, 28.2%  $\gamma$ -globulin. Bone marrow aspiration and biopsy demonstrated plasma cells constituted 6% of bone marrow cells. But she discontinued the treatment due to serious side effects. Then, she visited Nanjing University of Chinese Medicine clinic and turned to Doctor Huang Huang for help in May 2001. She does not have a family history of MM. She complained about sensation of pain and numbness, fatigue, hyperhidrosis, spontaneous perspiration, slight fever, chill, larynx mucosa ulcers, pharynx mucosa ulcers, and poor appetite. She looked ochriasis.

### 2.2. Diagnostic assessment and therapeutic intervention

Bone marrow aspiration and biopsy indicated bone marrow plasma cell counted 10%. Laboratory test showed hemoglobin of 76 g/L, IgG of more than 30 g/L. Emission computed tomography revealed the patient's left renal function was low. Serum immunofixation electrophoresis showed the presence of M-protein of the IgG-k type. According to the National Comprehensive Cancer Network Guidelines, the patient was diagnosed with MM. At the patient's first visit, her clinical symptoms were sensation of pain and numbness, fatigue, hyperhidrosis, spontaneous perspiration, slight fever, and chill. Based on the TCM theory, the patient's condition was categorized as Xue Bi. Monkshood, licorice and the classical Chinese prescription, HGWT composed of Radix Astragali, Ramulus cinnamomi, Radix Paeoniae Alba, Common Ginger Rhizome, Common Jujube Fruit, were employed to her. Monkshood was predecocted for 30 minutes, and licorice was used to reduce the potential toxicities. Soon, the symptom of spontaneous perspiration disappeared. Her temperature also returned to normal. Larynx mucosa ulcers and pharynx mucosa ulcers were greatly improved. In August 2001, the laboratory tests showed hemoglobin of 105 g/L, serum total protein of 84.1 g/L, serum albumin of 44.2 g/L, serum globulin of 39.9 g/L, creatinine of 63.8  $\mu$ mol/L, BUN of 7.2 mmol/L, IgG of 24.6 g/L. Serum protein electrophoresis showed 56% albumin, 2.5%  $\alpha$ 1-globulin, 7.2%  $\alpha$ 2-globulin, 9.2%  $\beta$ -globulin, 25.2%  $\gamma$ -globulin. Bone marrow aspiration and biopsy demonstrated plasma cells constituted 5.6% of bone marrow cells. The laboratory test indicated the patient's condition did not get worse after withdrew chemotherapeutic treatment. And the side effects of chemotherapy were under good control.

Up to now, the patient has been taking the Chinese herb medicine for 18 years. During this period, she insists on receiving TCM treatment alone. Prescription has been modified according to the main symptoms. The basic prescription is composed of Radix Astragali, Ramulus cinnamomi, Radix Paeoniae Alba, Common Ginger Rhizome, Common Jujube Fruit, Rhizoma Atractylodis Macrocephalae, Radix Saposhnikoviae, Poria Cocos, Rhizoma Alismatis, and Polyporus umbellatus. Actually, in addition to HGWT, the basic prescription includes another 2 classical Chinese prescriptions, Yu Ping Feng San (Radix Astragali, Rhizoma Atractylodis Macrocephalae, and Radix Saposhnikoviae) and Wu Ling San (Ramulus cinnamomi, Poria Cocos, Rhizoma Atractylodis Macrocephalae, Rhizoma Alismatis, Polyporus umbellatus). Monkshood would be added when the patient had sunken pulse, hyperhidrosis, and chill. Radix Angelicae Sinensis would be added when the patient had blood deficiency.

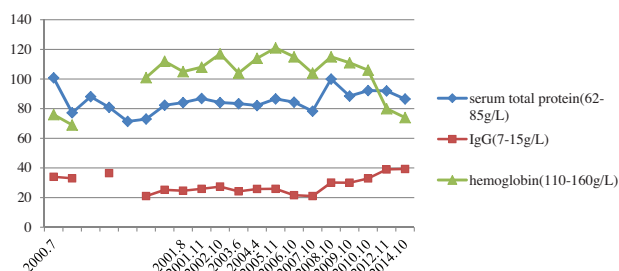
Both HGWT and Wu Ling San are classical Chinese prescriptions first recorded in Jin Kui Yao Lue. Wu Ling San was also recorded in Shanghan Lun. Jin Kui Yao Lue and Shanghan Lun were both written by Zhang Zhongjing around 2000 years ago. Yu Ping Feng San was recorded in Jiu Yuan Fang, written in Song dynasty. In Jin Kui Yao Lue, HGWT is the basic prescription for the treatment of Xue Bi. The main clinical symptoms of Xue Bi are body pain and numbness. At the patient's first clinic visit, she complained about sensation of pain, numbness and fatigue. Based on TCM theory, her clinical symptoms were categorized as Xue Bi. The patient with low immunity was prone to catching cold. So she was treated with Yu Ping Feng San, an effective prescription for hyperhidrosis, slight fever and chill. During the visit, because of renal insufficiency, the patient had mild edema in both lower limbs and over the face, dysuria and thirst. So Wu Ling San was used to deal with the water metabolism disorder. When monkshood was added, the

**Table 1****Herbs' dosage.**

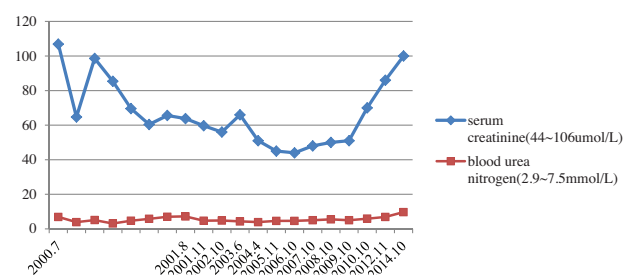
Chinese name	English name	Dosage, g
Huangqi	Radix Astragali	30–120
Guizhi	Ramulus cinnamomi	6–12
Baishao	Radix Paeoniae Alba	10–30
Fuling	Poria Cocos	12–40
Baizhu	Rhizoma Atractylodis Macrocephalae	10–30
Zexie	Rhizoma Alismatis	15–40
Zhuling	Polyporus umbellatus	10–30
Fangfeng	Radix Saposhnikoviae	6–20
Zhifupian	Monkshood	6–15
Gancao	Licorice	3–5
Shengjiang	Common Ginger Rhizome	5–10
Dazao	Common Jujube Fruit	20–50
Danggui	Radix Angelicae Sinensis	6–15

modified prescription included another classical Chinese prescription, Zhen Wu Tang (monkshood, Poria Cocos, Rhizoma Atractylodis Macrocephalae, Radix Paeoniae Alba, Common Ginger Rhizome), also recorded in Shanghan Lun. When Radix Angelicae Sinensis was added, the modified prescription also included another classical Chinese prescription, Danggui Buxue Tang (Radix Astragali and Radix Angelicae Sinensis). Danggui Buxue Tang was recorded in Nei Wai Shang Bian Huo Lun, written in Yuan dynasty. So the basic prescription was composed of several classical Chinese prescriptions. Because HGWT was the only prescription used in the early stage. HGWT is also the main prescription throughout the period of treatment. And some components of these prescriptions are the same traditional Chinese herb medicines. Then we named the basic prescription as modified HGWT.

The prescription was decocted with water. With changes of the patient's condition, the dosage and frequency of taking medicine altered, too (see Table 1 which illustrates the main herbs' dosage). If the clinical symptoms became worse and the patient had backache, limbs pain, abdominal pain, shortness of breath, and chest congestion, the decoction needed to oral a dose twice per day and the dosage would be increased. If the disease remained stable, frequency would be decreased to oral half dose once per day. Initially, the patient visited the clinic once every half or 1 month. Afterward, she visited the clinic once 2 or 3 months, even once half or 1 year. Because the prescription changed little, she took the medicine by herself in the last few years. There was a time, she stopped taking medicine for several months. Then she felt symptoms became worse. Laboratory tests indicated renal



**Figure 1.** Results of serum total protein, IgG, and hemoglobin. Results of these laboratory tests come from the patient's records and hospital files. In 2000, the hospital did not have perfect recording system. Though the patient recorded most detail information, some data lost.



**Figure 2.** Results of serum creatinine and blood urea nitrogen. Results of these laboratory tests come from the patient's records and hospital files.

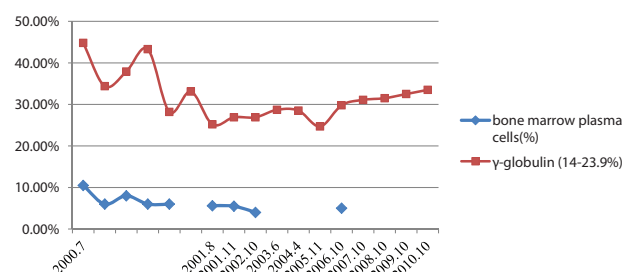
function reduced. After visiting the clinic, her symptoms improved. Since then, she never stopped taking the medicine again. Following Doctor Huang's advice, the patient has been eating Radix Astragali porridge or drinking Radix Astragali tea for 18 years.

### 2.3. Follow-up and outcomes

Follow-up laboratory tests indicated the patient's disease remained stable (see Figs. 1–3 which illustrate the results of main laboratory results). Last bone marrow aspiration and biopsy in October 2006 showed bone marrow plasma cell counted 5%. Last detailed laboratory tests in October 2014 showed hemoglobin of 74 g/L, serum total protein of 86.5 g/L, serum albumin of 36.1 g/L, serum globulin of 50.4 g/L, creatinine of 100 μmol/L, BUN of 9.7 mmol/L, IgG of 39.3 g/L. Serum free light chain-κ value was 38.1 g/L. Serum free light chain-λ value was 5.62 g/L. The κ/λ ratio was 6.77. The last laboratory tests showed some laboratory results rose again, but the patient felt good about herself and she insisted on accepting TCM treatment. The patient has experienced joint pain or backache sometimes. So she chose acupuncture as the adjuvant therapy at the same time. Routine physical examination results of the last 2 years showed the patient's disease remained stable. Though MM is not cured, her life quality is excellent (see Table, Supplemental Content, which illustrates timeline of the disease progression and the therapeutic measures, <http://links.lww.com/MD/B999>).

### 3. Discussion

Bone marrow microenvironment plays an important role on the pathogenesis of MM.<sup>[10]</sup> The interaction between MM cells and bone marrow microenvironment contributes to differentiation, migration, proliferation, survival, and drug resistance of the



**Figure 3.** Results of bone marrow plasma cells and γ-globulin. Results of these laboratory tests come from the patient's records and hospital files.

malignant plasma cells. Mesenchymal stem cells, dendritic cells, macrophages, osteoblasts, and osteoclasts are the important components of bone marrow microenvironment.<sup>[11]</sup> Chinese herb medicines and prescriptions, Radix Astragali, Rhizoma Atractylodis Macrocephalae, Polyporus umbellatus, and Yu Ping Feng San may play an important role in attenuating dysfunction of bone marrow microenvironment.

Bone marrow mesenchymal stem cells are abnormal in MM patients.<sup>[12,13]</sup> Bone marrow mesenchymal progenitor cell increases production of interleukin (IL)-1 $\beta$ , IL-6, granulocyte colony-stimulating factor, granulocyte macrophage, stem cell factor, and tumor necrosis factor (TNF)- $\alpha$ .<sup>[13]</sup> IL-6 which can promote the proliferation and survival of MM cells is regarded as one of the most important cytokines in MM disease progression.<sup>[14]</sup> But stimulating bone formation by injection of mesenchymal stem cells can inhibit MM cells growth.<sup>[15]</sup> Mesenchymal stem cells also can promote survival while inhibit proliferation and maturation of B cells.<sup>[16]</sup> Plasma cells normally arise from the differentiation of B cells. The pathogenesis of MM and B cells are closely related.<sup>[17]</sup> Radix Astragali can significantly enhance the proliferation of mesenchymal stem cells and transforming growth factor  $\beta$ 1 induced chondrogenic differentiation of mesenchymal stem cells.<sup>[18]</sup> Additionally, Astragalus polysaccharides isolated from Astragalus membranaceus can activate mouse B cells and macrophages via membrane Ig in a toll-like receptor (TLR) 4 independent manner in terms of proliferation or cytokine production.<sup>[19]</sup>

Dendritic cells may account for a critical role in inducing tumor-specific immune responses to against malignant plasma cells.<sup>[20]</sup> But dendritic cells are dysfunctional in MM patients. High levels of IL-6 could alter maturation of dendritic cells in MM.<sup>[21]</sup> Polysaccharides isolated from Astragalus membranaceus are able to stimulate dendritic cells maturation through increasing expression of CD40, MHC II, CD80, and CD86.<sup>[22]</sup> Isoliquiritigenin and liquiritigenin which are isolated from Astragalus membranaceus can significantly inhibit the production of IL-6 and IL-12 p40 stimulated by lipopolysaccharide in bone marrow derived dendritic cells. Isoliquiritigenin also has a moderate inhibition on LPS-induced TNF- $\alpha$  production.<sup>[23]</sup> Studies show that polyporus polysaccharide purified from Polyporus umbellatus can promote the activation and maturation of murine bone-derived dendritic cells via TLR4.<sup>[24]</sup>

Wnt antagonists, blockade of Runx2, and soluble factors such as IL-3 and IL-7 have an inhibitory effect on osteoblasts in MM.<sup>[25]</sup> But osteoblasts may regulate MM cells growth and survival by secreting IL-6 in coculture systems with MM cells and blocking TRAIL-mediated apoptosis of MM cells through the secretion of osteoprotegerin.<sup>[26,27]</sup> Receptor activator of NF- $\kappa$ B ligand (RANKL), macrophage inflammatory protein-1 $\alpha$ , IL-3, and IL-6 produced by MM cells can increase osteoclast activity and result in osteolytic bone lesions. Osteoclast activity also promotes MM cells growth.<sup>[28]</sup>

Calycosin isolated from Radix Astragali has inhibitory effects on osteolytic bone lesions. Study shows calycosin possesses osteogenic properties.<sup>[29]</sup> Calycosin also can inhibit osteoclast differentiation and bone resorption through suppressing RANKL-induced NF- $\kappa$ B and mitogen-activated protein kinases signaling pathways.<sup>[30]</sup> Rhizoma Atractylodis Macrocephalae is able to inhibit osteoclast differentiation by suppressing RANKL-induced sequential activation of NF- $\kappa$ B, c-Fos, and nuclear factor of activated T cells cytoplasmic 1 transcription factors in osteoclast precursors.<sup>[31]</sup> Atractylenolides isolated from Rhizoma Atractylodis Macrocephalae can induce mesenchymal stem cells

to differentiate into chondrocytes by increasing the expression of Sonic Hedgehog and its target gene Gli-1.<sup>[32]</sup> Throughout this period, the patient has experienced joint pain or backache sometimes. But osteolytic bone lesions had never been found. This may benefit from continuously taking the modified HGWT including Radix Astragali and Rhizoma Atractylodis Macrocephalae.

Macrophages also play an important role in promoting myeloma cell survival.<sup>[11]</sup> Polyporus umbellatus can strongly upregulate the functions of macrophages via TLR4 activation of signaling pathway. Polyporus umbellatus also can significantly increase the proliferation of splenocytes and stimulate the production of TNF- $\alpha$ , IL-1 $\beta$ , and nitric oxide of peritoneal macrophages from C3H/HeN mice.<sup>[33]</sup> Yu Ping Feng San composed of Radix Astragali, Rhizoma Atractylodis Macrocephalae, and Radix Saposhnikovia has bidirectional immunomodulatory effect in regulating the releases of cytokines from macrophages.<sup>[34]</sup>

Besides, pharmacological studies indicate that AI, one bioactive fractions extracted from the root of Astragalus membranaceus, could effectively suppress the activity of the macrophage-like tumors and the myeloid tumors.<sup>[35]</sup>

Animal trials indicate that Wu Ling San has a good effect on kidney stones.<sup>[36]</sup> For cancer patients in end-stage, Yu Ping Feng San is also a safe and effective treatment for idiopathic sweating of unknown cause.<sup>[37]</sup> Renal impairment is a common clinic feature of MM.<sup>[38]</sup> Astragalus membranaceus, Wu Ling San and Zhen Wu Tang have repair and protective effects on renal impairment.<sup>[39–41]</sup> Though the patient's renal function is low throughout these years, it has not worsened significantly. It may benefit from continuously taking the prescription including Radix Astragali, Wu Ling San, and Zhen Wu Tang. Studies show that Danggui Buxue Tang has inhibitory effects on bone marrow hematopoiesis suppression induced by Cyclophosphamide in mice by spurring the synthesis and secretion of hematopoietic growth factor and the proliferation of hematopoietic progenitor cells in mice.<sup>[42]</sup> It may have benefits on the patient's anemia.

Radix Astragali is the most important herb in modified HGWT. When the patient's condition worsened, its dosage was increased from 30 to 120g. Though the patient has taken the herbs for almost 18 years, no adverse reactions were observed. Radix Astragali and its effective components can significantly enhance the proliferation of mesenchymal stem cells, stimulate dendritic cells maturation, activate B cells and macrophages, decrease the production of IL-6, IL-12 p40, and TNF- $\alpha$ , promote bone formation and inhibit osteoclast differentiation and bone resorption. Rhizoma Atractylodis Macrocephalae also has inhibitory effects on osteolytic bone lesions. Polyporus umbellatus and its effective components can upregulate the functions of macrophages and promote the activation and maturation of murine bone-derived dendritic cells. Yu Ping Feng San also has bidirectional immunomodulatory effects in regulating the releases of cytokines from macrophages. So the modified HGWT may have potential in regulating the bone marrow microenvironment. Wu Ling San and Zhen Wu Tang have repair and protective effects on renal impairment. Danggui Buxue Tang is helpful for anemia. The prescription has multitargeted therapeutic effects on this MM patient's disease.

Beside the multitargeted therapeutic effects, low cost and small side effects, modified HGWT could potentially be beneficial for relieving the side effects of chemotherapy. These indicate Chinese herb medicines and TCM prescriptions could be promising for MM therapy. The Chinese herb medicines, especially Radix



Astragali, may have great potential in regulating the bone marrow microenvironment. More studies of Radix Astragali on MM are warranted.

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