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Influencing Factors on the clinical effect of yishenhuoxue detoxification method combined with bortezomib-lenalidomide-dexamethasone (VRD) regimen and radiotherapy in the treatment of multiple myeloma

M.S. Wang, Y.Q. Li*, E.C. Gao, Y.C. Zhou, H. Fan, Z.H. Zhou, S.L. Yang, C.Y. Sun

Second Department of Hematology, Langfang Traditional Chinese Medicine Hospital, Langfang, 065000, China

► ***Original article***

Corresponding author:
Yingqiao Li, M.D.
E-mail: *hengshuilyq@126.com*

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ABSTRACT

Background: To evaluate factors influencing the clinical efficacy of radiotherapy combined with the Yishenhuoxue detoxification (YSHX-D) method and the bortezomib-lenalidomide-dexamethasone (VRD) regimen in multiple myeloma (MM). ***Materials and Methods:*** From February 2021 to November 2022, 100 MM patients were enrolled in the Department of Hematology and Oncology at Langfang Traditional Chinese Medicine Hospital. Diagnosis was confirmed through bone marrow examination and immunological index analysis. Patients were randomly assigned to two groups (n=50 each). The observation group received radiotherapy with YSHX-D plus VRD, while the control group received radiotherapy with VRD alone. Radiotherapy was delivered to symptomatic bone lesions to relieve pain and stabilize disease progression. Clinical indicators included M protein, immunoglobulins, haemoglobin, platelets, and white blood cells. Treatment response was assessed per International Myeloma Working Group (IMWG) criteria. ***Results:*** Both groups achieved pain relief and slowed lesion progression with radiotherapy. The observation group demonstrated higher response rates than the control group, with greater reductions in M protein and immunoglobulins and improvements in haemoglobin and platelet counts ($P<0.05$). Logistic regression identified disease stage, age, genetic factors, and immune status as independent predictors of treatment efficacy. ***Conclusion:*** Radiotherapy combined with YSHX-D and VRD is safe and effective for MM, especially for managing skeletal complications. Patient-specific factors significantly influence outcomes, underscoring the need for individualized treatment strategies.

INTRODUCTION

Multiple myeloma (MM) is a malignant plasma cell disorder characterized by clonal proliferation within the bone marrow, excessive production of monoclonal immunoglobulins (M-proteins), and associated end-organ damage such as osteolytic lesions, fractures, and renal impairment [1-3]. It is most prevalent in adults over 60 years of age and remains incurable despite advances in therapy [4, 5].

Treatment options include chemotherapy, proteasome inhibitors, immunomodulatory agents, monoclonal antibodies, autologous stem cell transplantation, and radiotherapy [6]. Notably, radiotherapy's role in MM is being reexamined in the era of novel systemic therapies. A recent retrospective review of over 500 MM patients treated with RT revealed heterogeneous use patterns and emphasized the need for modern combining strategies [7]. Among these, radiotherapy remains essential for the palliation of painful bone lesions and prevention of skeletal-related events, significantly improving patient quality of life [8]. Despite therapeutic progress, recurrence and drug resistance continue to limit long-term outcomes [9]. Meanwhile, breakthroughs in MM treatment-including CAR-T therapy, bispecific antibodies, and advanced imaging modalities-have reshaped expectations for disease control and monitoring [10].

The bortezomib–lenalidomide–dexamethasone (VRD) regimen is a widely established standard therapy, achieving high response rates and survival benefits. At the same time, traditional Chinese medicine approaches such as the Yishenhuoxue detoxification (YSHX-D) method have been investigated for their potential to enhance hematopoietic recovery, reduce treatment-related toxicity, and complement modern regimens. Emerging mechanistic and integrative reviews suggest that TCM may synergize with proteasome inhibitors via pathways including NF-κB and apoptosis, and may influence the bone marrow microenvironment [11]. In a Taiwanese cohort, Chinese herbal medicine used ≥30 days was associated with improved survival in MM patients [12]. However, robust clinical evidence integrating YSHX-D with VRD and radiotherapy remains limited.

To address this gap, we designed a clinical study

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evaluating the combined application of radiotherapy, VRD, and YSHX-D in patients with MM. By systematically assessing hematological parameters, immunoglobulin responses, and clinical efficacy according to International Myeloma Working Group (IMWG) criteria, as well as identifying predictive factors through logistic regression analysis, we aimed to clarify the therapeutic value of this integrated approach.

The novelty of this study lies in its comprehensive evaluation of radiotherapy in combination with both VRD and YSHX-D, and its exploration of independent factors influencing treatment outcomes. To our knowledge, this is among the first clinical studies to investigate this triple-modality approach, providing evidence that may guide more individualized treatment strategies for MM.

MATERIALS AND METHODS

General information

From February 2021 to November 2022, one hundred patients diagnosed with multiple myeloma (MM) were enrolled in the Department of Hematology and Oncology at Langfang Traditional Chinese Medicine Hospital. Diagnosis was confirmed through bone marrow examination and immunological index analysis. Patients ranged in age from 43 to 69 years, with a mean age of 62.5 ± 5.4 years. The cohort included 68 males and 32 females. Patients were randomly assigned to two groups: 50 patients in the observation group and 50 in the control group.

Inclusion criteria: Eligible patients were between 18 and 70 years of age and had a diagnosis of MM based on the International Myeloma Working Group (IMWG) diagnostic criteria. All included cases were relapsed or refractory and not receiving first-line treatment. Patients had not received prior MM-related therapies outside those specified in this protocol, and all participants provided written informed consent.

Exclusion criteria: Patients were excluded if they had severe comorbid organ dysfunction (including cardiac, hepatic, or renal insufficiency) or active infections such as HIV. Pregnant or breastfeeding women were excluded, as were patients with coagulation abnormalities or bleeding tendencies, those with concurrent malignancies, and those participating in other clinical trials. Additional exclusions included documented allergy or intolerance to Yishenhuoxue detoxification (YSHX-D), the VRD regimen, or radiotherapy, as well as refusal to provide informed consent.

Ethics statement**:** The study was approved by the Ethics Committee of Langfang Traditional Chinese Medicine Hospital (Approval No. LF-TCMH-2021-45, registered 12 February 2021). All participants signed informed consent, and all procedures were performed in accordance with the Declaration of Helsinki and relevant national ethical guidelines.

Treatment interventions

All patients received four cycles of induction therapy, each lasting 28 days, consisting of the bortezomib–lenalidomide–dexamethasone (VRD) regimen combined with radiotherapy. The VRD regimen was as follows: lenalidomide (Revlimid, Celgene/BMS, USA) 25 mg orally once daily on days 1 -21 of each cycle; bortezomib (Velcade, Janssen, Belgium) 1.3 mg/m^2 subcutaneously on days 1, 8, and 22 (maximum 2 mg per dose); and dexamethasone (Generic, China) 40 mg orally once weekly on days 1, 8, 15, and 22. Patients in Revised International Staging System (R-ISS) stages I and II received lenalidomide maintenance, while those in stages III and IV received bortezomib maintenance.

All patients also received supportive care: zoledronic acid (Zometa, Novartis, Switzerland; 4 mg intravenously every 4 weeks) to protect bone health, acyclovir (GlaxoSmithKline, UK; 400 mg orally twice daily) to prevent herpes zoster infection, and aspirin (Bayer, Germany; 75 mg orally once daily) for thrombosis prophylaxis, unless contraindicated.

Radiotherapy protocol

Radiotherapy was delivered to both groups to target symptomatic bone lesions for pain relief and stabilization of skeletal damage. External beam radiotherapy (EBRT) was administered using a Varian TrueBeam linear accelerator (Varian Medical Systems, Palo Alto, CA, USA). A total dose of 30 Gy was prescribed in 10 fractions of 3 Gy each, delivered over two weeks (five fractions per week). For spinal lesions, intensity-modulated radiotherapy (IMRT) was used to minimize spinal cord exposure, with a maximum cord dose of 18 Gy. Treatment planning was performed using Eclipse software (Varian Medical Systems, USA), ensuring that at least 95% of the planning target volume (PTV) received the prescribed dose. The average dose rate was 200-300 cGy/min. Radiotherapy was initiated concurrently with the first cycle of VRD chemotherapy.

Patients in the observation group additionally received YSHX-D herbal decoction (500 mL/day), prepared by the hospital pharmacy, administered orally for three consecutive weeks during each cycle. The formula was designed to support kidney function, promote blood circulation, and aid detoxification.

Assessment of myeloma-related indicators

Levels of M protein and immunoglobulins (IgA, IgG, IgM) were measured before and after treatment. Protein electrophoresis was performed using the Sebia Hydrasys 2 system (Sebia, France), and immunoglobulin levels were quantified using

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immunoturbidimetric assays (Roche Diagnostics, Mannheim, Germany). The degree of decline for each marker was calculated as:

Degree of decline = (Pre-treatment value – post-treatment value) / Pre-treatment value ×100 (%)

Blood cell testing

Fasting venous blood samples were collected on the morning of the first day of each cycle into tubes containing 0.2 mL sodium heparin (BD Vacutainer, USA). Hemoglobin, platelet, and white blood cell counts were measured using a Sysmex XN-Series automated hematology analyzer (Sysmex Corporation, Kobe, Japan).

Clinical efficacy evaluation

Treatment responses were evaluated according to IMWG criteria. A complete response (CR) was defined as the absence of detectable disease in both clinical and laboratory examinations; partial response (PR) was defined as a substantial reduction in disease burden with residual disease present; stable disease (SD) indicated no significant disease progression or regression; and progressive disease (PD) was defined as the appearance of new or worsening lesions. Responses were assessed at the end of treatment, with imaging evaluation of bone lesions by PET-CT or MRI, and pain severity recorded using the Visual Analog Scale (VAS).

Statistical analysis

All statistical analyses were conducted using GraphPad Prism version 6.1 (GraphPad Software, San Diego, CA, USA). Continuous variables were expressed as mean ± standard deviation (SD). Group comparisons were performed using Student's t-test or analysis of variance (ANOVA) as appropriate, while categorical variables were compared using the chi-square test. Logistic regression analysis was performed to identify independent factors associated with treatment outcomes. A p-value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

As shown in table 1, baseline characteristics were comparable between groups, with no statistically significant differences. In the control group (radiotherapy with VRD), the male-to-female ratio was 33:17, whereas in the observation group (radiotherapy with YSHX-D and VRD) it was 35:15. The mean age of patients in the control group was 61.8 ± 5.3 years compared with 63.2 ± 6.6 years in the observation group. Body mass index (BMI) was similar between groups (21.8 ± 2.4 vs. 22.3 ± 2.0 kg/m^2). Distribution by International Staging System (ISS) stage also showed no significant differences: 16% vs. 22% in ISS-I, 44% vs. 42% in ISS-II, and 40% vs. 36% in ISS-III (all P > 0.05). Smoking and drinking habits were also balanced between groups (P > 0.05). These results confirm that randomization produced two comparable cohorts.

Table 1. Baseline characteristics of patients in the control and observation groups. Data are presented as mean ± SD or n (%). BMI = body mass index; ISS = International Staging System.

Characteristic	Control group (n=50)	Observation group (n=50)	t / χ^2 value	P-value
Gender (male: female)	33:17	35:15	3.178	0.358
Age (years)	61.76 ± 5.34	63.18 ± 6.62	2.003	0.212
BMI (kg/m^2)	21.76 ± 2.36	22.34 ± 1.96	4.197	0.166
ISS-I (%)	8 (16.0%)	11 (22.0%)	1.226	0.215
ISS-II (%)	22 (44.0%)	21 (42.0%)	4.288	0.449
ISS-III (%)	20 (40.0%)	18 (36.0%)	3.416	0.268
Smoking (%)	11 (22.0%)	9 (18.0%)	2.007	0.314
Drinking (%)	15 (30.0%)	17 (34.0%)	1.885	0.449

Reduction in myeloma-related indicators

Patients in the observation group experienced significantly greater reductions in M-protein and immunoglobulin levels compared with the control group. The decline in M-protein was 30.5 ± 4.4% in the observation group versus 14.3 ± 2.6% in the control group (P = 0.003). Similarly, IgA, IgG, and IgM levels declined more in the observation group (20.4 ± 3.1%, 27.3 ± 5.5%, and 33.3 ± 4.2%, respectively) than in the control group (10.3 ± 2.5%, 18.4 ± 4.3%, and 22.1 ± 3.7%, all P < 0.05) (table 2).

Table 2. Reduction (%) in M-protein and immunoglobulins after treatment. Data are mean ± SD.

Group	M-protein (%)	IgA (%)	IgG (%)	IgM (%)
Control (n=50)	14.33±2.61	10.34±2.45	18.35±4.29	22.13±3.66
Observation (n=50)	30.46±4.39	20.38±3.11	27.33±5.47	33.26±4.18
χ^2-value	12.402	9.375	10.246	13.839
P-value	0.003	0.016	0.023	0.005

Hematological parameters

Post-treatment hemoglobin and platelet counts were significantly higher in the observation group compared with the control group (P <0.05), while leukocyte counts showed no significant difference (table 3).

Table 3. Post-treatment hematological indices. Data are mean ± SD.

Group	Hemoglobin (g/dL)	Platelets (×10^4/μL)	Leukocytes (×10^3/μL)
Control (n=50)	13.24 ± 2.56	24.58 ± 3.18	10.54 ± 2.44
Observation (n=50)	19.57 ± 3.27	53.26 ± 5.26	4.37 ± 1.79
χ^2-value	10.324	13.671	9.004
P-value	0.014	0.006	0.023

Clinical response rates

According to IMWG criteria, the observation group achieved significantly higher complete response (28.0% vs. 10.0%, P = 0.003) and partial response (52.0% vs. 34.0%, P = 0.024) rates than the control group. Stable disease and progressive disease were more frequent in the control group (38.0% and 18.0%) than in the observation group (12.0% and 8.0%) (P < 0.05 for both) (table 4). Radiotherapy contributed to significant improvements in bone

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pain, as confirmed by reduced Visual Analog Scale scores, and regression of bone lesions was confirmed by PET-CT/MRI.

Table 4. Clinical response rates per IMWG criteria. CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

Group	CR (%)	PR (%)	SD (%)	PD (%)
Observation (n=50)	14(28.0%)	26(52.0%)	6(12.0%)	4(8.0%)
Control (n=50)	5(10.0%)	17(34.0%)	19(38.0%)	9(18.0%)
χ^2-value	9.627	13.605	11.341	10.786
P-value	0.003	0.024	0.015	0.006

Adverse reactions

As shown in table 5, the overall incidence of adverse reactions did not differ significantly between groups (22% in the observation group vs. 20% in the control group, P>0.05). The most common adverse events were nausea/vomiting, myelosuppression, dizziness/fatigue, immune suppression, and liver/kidney dysfunction. Radiotherapy-related skin reactions were minimal and comparable.

Multifactorial analysis of outcomes

Logistic regression analysis identified disease stage, patient age, genetic factors, and immune system status as independent predictors of clinical outcome. Higher disease stage, advanced age, adverse genetic markers, and impaired immune status were significantly associated with poorer treatment response (table 6).

Table 5. Incidence of treatment-related adverse reactions. Data are n (%).

Group	Nausea/vomiting (%)	Myelosuppression (%)	Dizziness/fatigue (%)	Immune suppression (%)	Liver/kidney dysfunction (%)
Observation (n=50)	1 (2.0%)	2 (4.0%)	2 (4.0%)	3 (6.0%)	3 (6.0%)
Control (n=50)	2 (4.0%)	1 (2.0%)	3 (6.0%)	2 (4.0%)	2 (4.0%)
χ^2-value	3.102	4.119	2.046	3.174	3.445
P-value	0.294	0.441	0.326	0.449	0.218

Table 6. Logistic regression analysis of factors influencing treatment outcomes. OR = odds ratio; CI = confidence interval.

Variable	OR	95% CI	P-value
Disease stage	1.62	1.03-2.15	0.034
Patient age	1.47	1.12-2.44	0.017
Genetic factors	1.53	1.05-1.99	0.006
Immune status	1.57	1.27-1.86	0.025

DISCUSSION

Multiple myeloma (MM) is a hematological malignancy marked by clonal proliferation of plasma cells, leading to impaired hematopoiesis, bone destruction, and production of excessive monoclonal immunoglobulins [13-17]. Bone involvement, especially in the spine, ribs, and hips, contributes substantially to morbidity [18, 19], and the etiology is influenced by both genetic and environmental factors [20, 21]. While current therapies include chemotherapy, immunotherapy, transplantation, and radiotherapy [22, 23], optimizing treatment combinations remains critical.

In this study, we evaluated the effect of radiotherapy combined with Yishenhuoxue detoxification (YSHX-D) and the VRD regimen on clinical outcomes in MM patients. Radiotherapy, delivered as EBRT at 30 Gy in 10 fractions, provided effective palliation of bone lesions. Patients receiving the combined YSHX-D and VRD regimen showed significantly greater reductions in M protein and immunoglobulin levels than those treated with VRD and radiotherapy alone. These findings suggest that YSHX-D, which supports kidney function, circulation, and detoxification , may enhance systemic tumor burden reduction when added to established regimens [24]. Similarly, the VRD regimen-recognized as a standard therapeutic backbone [25-27] - likely synergized with radiotherapy to improve outcomes [28].

Beyond biochemical indicators, patients in the observation group demonstrated higher rates of complete and partial responses, along with improvements in hemoglobin and platelet counts. These outcomes highlight the dual contribution of radiotherapy in stabilizing bone marrow function and YSHX-D in supporting hematopoiesis [29]. Importantly, adverse reactions did not significantly differ between groups, indicating that the addition of YSHX-D did not increase treatment toxicity. Logistic regression further confirmed that disease stage, age, genetic factors, and immune status significantly influenced treatment efficacy, consistent with the multifactorial nature of MM prognosis [30].

Several limitations should be acknowledged. The sample size was modest and limited to a single center, which may restrict generalizability. Follow-up was short, focusing on short-term outcomes rather than long-term survival, and molecular mechanisms underlying YSHX-D's effects were not investigated. Nevertheless, these findings provide important clinical evidence supporting integration of radiotherapy and traditional Chinese medicine with standard systemic therapy in MM.

CONCLUSION

Radiotherapy combined with YSHX-D and the VRD regimen was safe and more effective than radiotherapy with VRD alone for patients with MM, particularly in controlling bone lesions and enhancing treatment responses. Clinical efficacy was influenced by patient-specific factors such as disease stage, age, genetic background, and immune status, underscoring the need for personalized treatment

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strategies. Larger, multi-center studies with extended follow-up are warranted to confirm and expand upon these results.

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***Conflict of interest*:** The authors declare that there are no conflicts of interest related to this study or its publication.

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***Ethical considerations*:** This study was reviewed and approved by the Ethics Committee of Langfang Traditional Chinese Medicine Hospital (Approval No. LF-TCMH-2021-45, registered 12 February 2021). Written informed consent was obtained from all participants before enrollment. The study was conducted in compliance with the Declaration of Helsinki and national ethical regulations.

***Authors' contributions*:** M.W. was responsible for conceptualization, study design, data curation, and preparation of the first draft of the manuscript. Y.L., as the corresponding author, supervised the project, ensured compliance with research protocols, and contributed to reviewing and editing the manuscript. E.G., Y.Z., and H.F. contributed to patient management and clinical data collection. Z.Z. and S.Y. conducted laboratory testing and data validation. C.S. carried out the statistical analysis and contributed to manuscript preparation. All authors reviewed and approved the final version of the manuscript.

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