



# Glutathione combined with mecobalamin in the treatment of chemotherapy-induced peripheral neuropathy in multiple myeloma: a retrospective clinical study

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**Background:** This study sought to examine the use of glutathione combined with mecobalamin in the prevention and treatment peripheral neuropathy (PN) in multiple myeloma (MM) patients, observe its effectiveness and safety, and explore the risk factors and prognostic factors of chemotherapy-induced peripheral neuropathy (CIPN).

**Methods:** Patients in the study group were administered 2.4 g of glutathione intravenously once daily 2–3 days before chemotherapy, combined with 500 µg of mecobalamin administered intravenously once every other day until the end of the chemotherapy cycle. Patients who did not use this regimen were selected as a control group. Differences in adverse reactions, treatment efficiency, progression-free survival (PFS), and overall survival (OS) between the two groups were retrospectively analyzed. PFS and OS curves were plotted using the Kaplan-Meier method. The univariate analysis rates were compared using the  $\chi^2$  test. The multivariate analysis was performed by a logistic regression analysis. The proportional hazard regression model was used for the univariate and multivariate proportional hazards model analyses.

**Results:** The incidence of PN, especially grade 2 and 3 PN, was more decreased in the study group than the control group. The history of diabetes ( $P=0.032$ ) and the method of bortezomib injection ( $P=0.043$ ) was found to affect the PN grade. The multivariate logistic regression analysis showed that diabetes was an independent risk factor of PN in MM patients [odds ratio (OR) =3.484,  $P=0.020$ ]. The Proportional hazards model multivariate analysis showed that extramedullary disease (EMD) [hazard ratio (HR) =2.373,  $P=0.006$ ] and elevated lactic dehydrogenase (LDH) (HR =1.934,  $P=0.009$ ) were independent prognostic factors for MM patients.

**Conclusions:** Glutathione combined with mecobalamin significantly reduced the incidence and severity of CIPN in MM patients, and did not increase the adverse reactions of patients with MM. Diabetes and bortezomib intravenously increased the incidence and severity of PN in patients with MM.

**Keywords:** Multiple myeloma (MM); glutathione; methylcobalamin; neuropathy

Submitted Sep 30, 2021. Accepted for publication Nov 29, 2021.

doi: 10.21037/apm-21-3313

View this article at: <https://dx.doi.org/10.21037/apm-21-3313>

## Introduction

The promotion of stem cell transplantation technology and the emergence of new treatment methods, including proteasome inhibitors and immunomodulators, have increased the survival time of MM patients (1-3). Despite increased life spans, PN complications and chemotherapy-induced peripheral neuropathy (CIPN) in MM associated with immunomodulators has attracted attention (4-6). Presently, CIPN caused by bortezomib or thalidomide-based chemotherapy regimens is the most common non-hematological, dose-limiting adverse reaction in MM patients, and significantly reduces their quality of life and survival. Thalidomide-related neurotoxicity occurs in 40% of patients (7), and is frequently characterized by paresthesia and loss of touch and pain. Potential mechanisms include degeneration of dorsal root ganglion, inhibition of angiogenesis and downregulation of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) which leading to Wallerian degeneration and loss of myelinated fibers (8,9). Bortezomib could damage dorsal root ganglion, mitochondrial and endoplasmic reticulum, inhibit the transcription of nerve growth factor (10). Usually causes painful sensory neuropathy, which commonly presents as a sharp or burning pain in the feet and fingertips, and autonomic dysfunction in 10% of patients (11). Among patients treated with bortezomib, 60–75% showed a complete reversal of symptoms at the 6-month follow-up examination, but only 25% thalidomide-treated patients showed remission (12,13).

Treatment for CIPN is limited. Reducing chemotherapy doses or treatment cycles can partially improve the neurological symptoms associated with MM; however, these measures also inevitably negatively affect MM treatment. Thus, more effective and safer neuroprotective methods urgently need to be identified. Glutathione is known to prevent the accumulation of toxic substances in the peripheral nervous system. The rich sulfhydryl groups of glutathione affect cell metabolism by activating enzymes promoting metabolism. In addition, a combination of sulfhydryl groups and oxygen free radicals increases the excretion of the oxygen free radical, further alleviating the neurotoxic side effects and producing no obvious effects on the efficacy of the chemotherapeutic drug (14). Mecobalamin is an endogenous vitamin B12 that has a high affinity for nervous tissues and can regulate the metabolism of various substances by stimulating lecithin and acetylcholine synthesis. Mecobalamin is generally used in the clinic in the treatment of neurological diseases (15).

Nowadays, there is no report about the efficacy of glutathione combined with mecobalamin on the treatment of MM patients with CIPN. In this study, we retrospectively analyzed the preventive and therapeutic effects of glutathione combined with mecobalamin on MM-related PN to determine whether this combination could be alleviates CIPN.

We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/apm-21-3313>).

## Methods

### *Research subjects*

A total of 158 MM patients diagnosed at the Affiliated Cancer Hospital of Zhengzhou University from September 2008 to September 2018 were selected as the study subjects, who were selected based on baseline data. To be eligible for enrollment in this study, patients had to meet the following inclusion criteria: (I) be aged  $\geq 18$  years; (II) have undergone disease diagnosis, classification, and Durie-Salmon (DS) and International Staging System (ISS) staging as per the 2017 Guidelines for the Diagnosis and Treatment of Multiple Myeloma in China; (III) have Eastern Cooperative Oncology Group physical fitness scores of 0, 1, or 2; (IV) have complete information available about their chemotherapy regimen, adverse reactions, examination results, and medical orders; and (V) have completed at least 2 cycles of chemotherapy. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had been diagnosed and treated at other hospitals; (II) had not responded to follow-up telephone calls and or had incomplete medical records; (III) had severe cardiac dysfunction or hepatic insufficiency; (IV) had other malignant solid tumors or hematological tumors; and/or (V) had shown poor compliance with medical advice.

### *Research methods*

In order to reduce CIPN, we take this combination regimen as a preventive measure that administrate it before chemotherapy. Patients were divided into a study group and a control group, and a retrospective analysis was conducted using the method of the control study. Patients in the study group were administered 2.4 g of glutathione intravenously once daily 2–3 days before chemotherapy, combined with 500  $\mu\text{g}$  of mecobalamin administered intravenously once

every other day until the end of the chemotherapy cycle. Patients in the control group were not administered glutathione or mecobalamin; however, when hepatic insufficiency occurred, liver-protecting drugs other than glutathione could be selected. The patients were divided into a bortezomib-exposed or bortezomib-unexposed group. The bortezomib-exposed group was further divided into an intravenous and a subcutaneous group based on how the bortezomib was injected. The bortezomib regimens included PD (bortezomib, dexamethasone), PAD (bortezomib, dexamethasone, doxorubicin), and PCD (bortezomib, cyclophosphamide, dexamethasone), while the bortezomib-free regimens included VAD (vindesine, doxorubicin, dexamethasone), DICE (dexamethasone, isocyclophosphamide, etoposide, cisplatin), hyper-CVAD (cyclophosphamide, longSpringdesin, epirubicin, dexamethasone), and DT-PACE (dexamethasone, thalidomide, etoposide, cisplatin, cyclophosphamide, epirubicin). We measure symptoms, signs, ability aspects, and electro-physiologic in MM patients by the Total Neuropathy Score (TNS), which was suggest as a reliable method for assessing both the severity and course of CIPN (16-18). All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics board of Affiliated Cancer Hospital of Zhengzhou University (No. 2020021301). Informed consent was taken from all the patients.

### *Adverse reactions*

During treatment, blood biochemistry (liver, renal, and coagulation functions and electrolytes), electrocardiograms, and imaging examinations were routinely performed for all patients. If hepatic insufficiency occurred, patients in the study group were given oral medicine to enhance the hepatoprotective effects, and patients in the control group were intravenously administered hepatoprotective drugs other than glutathione. If PN occurred, specific treatments were administered based on the severity of the reaction. If cytopenia occurred, granulocyte colony stimulating factor (G-CSF) or component blood transfusions were administered. If gastrointestinal symptoms occurred, antiemetic, acid suppression, gastrointestinal motility, and other drugs were administered. If creatinine clearance increased, symptomatic kidney protection treatment was administered, and hemofiltration or dialysis was performed as necessary. If a patient experienced a fever,

an anti-infection treatment was first administered and then pathogenic examination was performed to treat the symptoms.

### *Efficacy evaluation and follow-ups*

The Guidelines for the Diagnosis and Treatment of Multiple Myeloma in China (revised in 2017) were used as the evaluation criteria. Patients were followed up with by telephone calls or at clinic visits. The final follow-up date was September 1, 2018. The median follow-up period was 27.4 (1.9–100.7) months. The basic clinical data, adverse reactions, PFS, and OS of the groups were analyzed.

### *Statistical analysis*

The data analysis was performed using SPSS 21.0 statistical software. For the general data, non-parametric tests of two independent samples were used to evaluate the quantitative data, and the  $\chi^2$  test was used to evaluate the qualitative data. The  $\chi^2$  test and the Fisher exact probability method were used to compare effective rates. The univariate analysis rates were compared using the  $\chi^2$  test. The multivariate analysis was performed by a logistic regression analysis. PFS and OS curves were plotted using the Kaplan-Meier method, and the differences between the groups were compared using the Log-rank test. The proportional hazard regression model was used for the univariate and multivariate regression analyses, and differences were noted as statistically significant when the P value was <0.05.

## **Results**

### *Normal information*

In total, 158 patients were enrolled in this study. The study group comprised 114 (72.2%) patients [68 male and 46 female with a median age of 63 (range, 29–81) years]. In the study group, there were 64 IgG type patients, 26 IgA type patients, and 24 patients with other types, which concluded IgD type, IgM type, light chain type and non-secretory type. 18 patients (15.8%) showed extramedullary invasion, and 24 patients (21.1%) had diabetes. 97 patients (85.1%) were included in the bortezomib exposure group. The basic clinical data of all the patients included in the study and control groups are shown in *Table 1*, and there were no significant differences between the two groups ( $P>0.05$ ). There were 26 (22.8%) stage I patients in the study group,

**Table 1** Comparison of clinical data of the two groups of patients

Clinical features	Study group (n=114)	Control group (n=44)	$\chi^2$	P value
Gender			0.039	1.000
Male	68	27		
Female	46	17		
Age (years)			0.146	0.202
$\geq 60$	66	31		
$< 60$	48	13		
Immunophenotyping			3.630	0.163
IgG	64	26		
IgA	26	14		
Other types	24	4		
Extramedullary invasion			0.500	0.618
Yes	18	5		
No	96	39		
Diabetes			0.287	0.670
Yes	24	11		
No	90	33		
LDH (U/L)	258 [123–873]	236 [106–757]	-1.357	0.175
$\beta 2$ microglobulin (mg/dL)	5.1 [3.0–8.8]	5.2 [3.4–8.6]	-0.141	0.890
Plasma cell ratio (%)	33 [12–54]	33 [15–43]	-0.003	0.958
Chemotherapy regimen			0.709	0.473
Bortezomib-exposed group	97	35		
Bortezomib-unexposed group	17	9		
Bortezomib usage			0.873	0.428
Subcutaneous injection	56	17		
Intravenous injection	41	18		
ISS staging				
I	26	9		
II	40	13	0.817	0.665
III	48	22		
DS staging				
I + II	26	5	2.636	0.122
III	88	39		

but only 9 (20.5%) in the control group. There were 40 (35.1%) stage II patients in the study group, but only 13 (29.5%) in the control group. There were 48 (42.1%) stage III patients in the study group, but only 22 (50.0%) in the control group. No significant differences were noted in ISS staging between each group ( $P=0.665$ ). There were 26 stage I + II (22.8%) patients in the study group, but only 5 (11.4%) in the control group. There were 88 stage III (77.2%) patients in the study group, but only 39 (88.6%) in the control group. No significant differences in DS staging were found between the groups ( $P=0.122$ ; see *Table 1*).

### *Efficacy evaluation*

The remission rates of complete response (CR) and very good partial response (VGPR) were 18.4% and 15.9% in the study and control groups, respectively ( $P=0.819$ ). The remission rates of partial response (PR) in the study and control groups were 51.7% and 47.7%, respectively ( $P=0.724$ ). The overall response rate (ORR) of the study and control groups were 71.2% and 63.6%, respectively ( $P=0.450$ ).

### *Adverse reactions*

There were no significant differences in the adverse reactions, such as leukopenia, thrombocytopenia, hemoglobin reduction, pulmonary infection/upper respiratory tract infections, digestive tract symptoms, herpes zoster or urinary tract infections, between the study and control groups ( $P>0.05$ ). The incidence of PN was lower in the study group than the control group (31.6% *vs.* 41.7%), and the difference between grades 2 and 3 PN was statistically significant ( $P=0.048$  and  $P=0.040$ , respectively). The proportions of patients showing hepatic insufficiency in the study and control groups were 19.3% and 36.4%, respectively, and the difference was statistically significant ( $P=0.037$ ).

In the analysis of the factors affecting neuropathy, PN was characterized as a dependent variable, while gender, age, immune classification, extramedullary invasion, diabetes mellitus, bortezomib exposure, and the bortezomib injection method were characterized as independent variables. The results showed that the proportion of MM patients with diabetes who developed PN during treatment was significantly increased compared with non-diabetes MM patients ( $P=0.016$ ). PN was then classified into grades 1–5 (see *Table 2*), and a history of diabetes ( $P=0.032$ ) and

the method of bortezomib injection ( $P=0.043$ ) was found to affect the PN grade. A further analysis revealed that whether comorbid diabetes ( $P=0.010$ ) or the route of injection of bortezomib ( $P=0.008$ ) are associated with the incidence of grade 1 PN.

The logistic regression analysis of the diabetes and bortezomib injection methods revealed that the risk of PN in MM patients with diabetes was 3.484 times higher than that in patients without diabetes mellitus [95% confidence interval (CI): 1.214–10.003]. There was no significant difference in the risk of PN in MM patients when bortezomib was injected using different methods ( $P>0.05$ ; see *Table 3*).

A further analysis revealed that the incidence of PN was lower in patients with diabetes or those who received bortezomib intravenous injections in the study group than in the control group, but the difference was not statistically significant ( $P>0.05$ ). Glutathione combined with mecobalamin had no significant effect on PN in MM patients with diabetes or those who received bortezomib intravenous injections.

### *Subsistence analysis*

The median follow-up period was 27.4 (1.9–100.7) months. The median OS time was 49.2 months (95% CI: 35.2–59.4 months) in the study group and 51.3 months (95% CI: 35.7–68.9 months) in the control group. There was no significant difference in OS between the study and control groups ( $P=0.808$ ; see *Figure 1A*). The median PFS time was 24.6 months (95% CI: 14.1–35.0 months) in the study group and 26.8 months (95% CI: 19.0–40.6 months) in the control group. Similar to OS, there was no significant difference in PFS between the study and control groups ( $P=0.719$ ; see *Figure 1B*).

### *MM prognostic factors*

The univariate proportional hazards model revealed that the prognosis of MM was correlated with extramedullary disease (EMD) and elevated LDH ( $P<0.05$ ). Two factors found to affect prognosis were elevated EMD and LDH (see *Tables 4, 5*). The mortality risk of MM patients with EMD was 2.373 times higher than that of non-MM patients (95% CI: 1.282–4.393), and the median OS of MM patients with EMD and non-MM patients was 23.4 and 52.3 months, respectively (see *Figure 2A*). The mortality risk of patients with elevated LDH was 1.934 times higher than that of patients with normal LDH levels (95% CI: 1.179–3.173),

**Table 2** Factors affecting the severity of PN in MM

Clinical characteristics	Grade 1 (n=35)	Grade 2 (n=13)	Grade 3 (n=8)	Grade 4 (n=1)	$\chi^2$	P value
Gender					1.596	0.660
Male	21	6	5	1		
Female	14	7	3	0		
Age (years)					0.907	0.824
$\geq 60$	24	8	6	1		
$< 60$	11	5	2	0		
Immunophenotyping					4.044	0.671
IgG	20	7	4	1		
IgA	10	3	4	0		
Other types	5	3	0	0		
Extramedullary invasion					1.718	0.633
Yes	4	3	2	0		
No	31	10	6	1		
Diabetes					8.824	0.032
Yes	7	6	5	1		
No	28	7	3	0		
Chemotherapy regimen					0.280	0.964
Bortezomib-exposed group	31	11	7	1		
Bortezomib-unexposed group	4	2	1	0		
Bortezomib usage					8.157	0.043
Subcutaneous injection	19	3	1	0		
Intravenous injection	12	8	6	1		
DS staging					1.909	0.592
I + II	8	1	1	0		
III	27	12	7	1		
ISS staging					3.563	0.736
I	7	3	0	0		
II	11	5	3	0		
III	17	5	5	1		

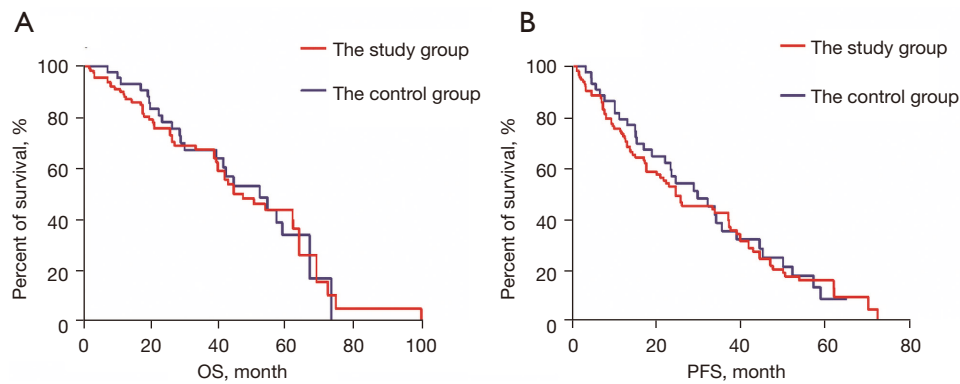
PN, peripheral neuropathy; MM, multiple myeloma.

**Table 3** Multivariate logistic regression analysis of PN in MM patients

Factors	B value	Standard error	Wald	P value	OR	95% CI
Diabetes	1.248	0.538	5.382	0.020	3.484	1.214–10.003
Bortezomib usage	−0.121	0.458	0.069	0.792	0.886	0.361–2.176

PN, peripheral neuropathy; MM, multiple myeloma; OR, odds ratio; CI, confidence interval.





**Figure 1** Kaplan-Meier estimates of overall survival (OS) and progression-free survival (PFS). (A) Kaplan-Meier survival curves of OS for study and control group; (B) Kaplan-Meier survival curves of PFS for study and control group.

**Table 4** Univariate proportional hazards model of factors affecting OS in MM

Factors	HR	95% CI	P value
Age	1.245	0.718–2.162	0.435
Gender	0.730	0.415–1.285	0.275
Immunophenotyping	0.931	0.644–1.345	0.702
EMD	1.966	1.088–3.552	0.025*
Diabetes	1.224	0.873–1.716	0.240
Elevated LDH	1.679	1.043–2.702	0.033*
Plasma cell ratio	0.965	0.555–1.679	0.899
Application of bortezomib	1.091	0.608–1.960	0.770
DS staging	1.240	0.721–2.131	0.437
ISS staging	0.730	0.458–1.165	0.187

\* indicates statistical significance. OS, overall survival; MM, multiple myeloma; HR, hazard ratio; CI, confidence interval; EMD, extramedullary disease; LDH, lactic dehydrogenase.

**Table 5** Prognostic factors of MM by multivariate proportional hazards model

Factors	Regression coefficient	Standard error	Wald	P value	HR	95% CI
EMD	0.864	0.314	7.569	0.006	2.373	1.282–4.393
LDH	0.660	0.253	6.819	0.009	1.934	1.179–3.173

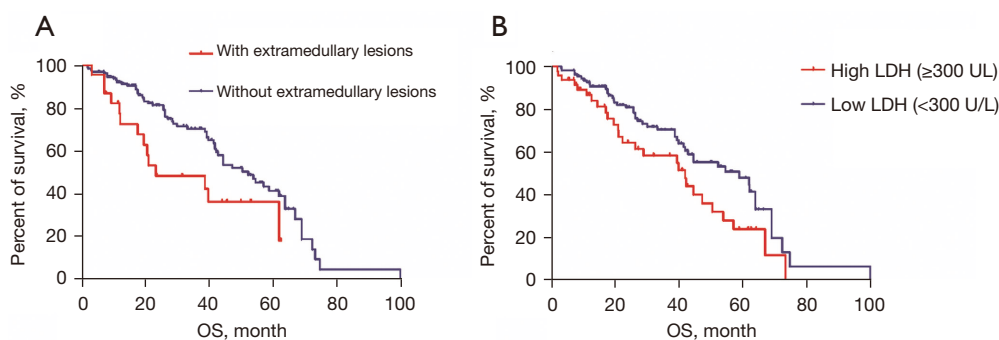
MM, multiple myeloma; HR, hazard ratio; CI, confidence interval; EMD, extramedullary disease; LDH, lactic dehydrogenase.

and the median OS of MM patients with EMD and without EMD was 41.9 and 58.9 months, respectively (see *Figure 2B*).

## Discussion

In this study, the male-to-female ratio was 1.5:1, suggesting

that the incidence of MM is higher in males than females. The age of onset ranged from 29 to 81 years, with a median age of 63 years, and a peak age of onset between 55–68 years of age. In our study, 27 (17.1%) MM patients were aged >70 years, and only 6 (3.8%) MM patients were aged <40 years, which differs to the median age of MM patients



**Figure 2** Prognostic factors for overall survival (OS) in multiple myeloma (MM) patients. (A) Effects of extramedullary disease (EMD) on OS in MM patients; (B) effects of lactic dehydrogenase (LDH) on OS in MM patients.

reported in other studies in China (19,20). In terms of clinical efficacy, the remission rates of VGPR were 18.4% and 15.9% in the study and control groups, respectively. The PR and ORR remission rates were 51.7% and 47.7%, and 71.2% and 63.6% for the study and control groups, respectively. There were no statistically significant differences between the groups. The curative effect of the study group was better than that of the control group, which may be related to there being a slightly lower proportion of clinical stage III patients in the study group than the control group. In addition, the incidence and severity of PN were better in the study group than in the control group, suggesting that reducing the dose of chemotherapy or the treatment cycle would improve the occurrence of PN and thus mitigating toxicities in the treatment of MM (21,22).

Many experimental studies have examined the mechanisms behind CIPN. Poruchynsky *et al.* suggested that bortezomib increases microtubule aggregation and hinders signaling by affecting the proteins that regulate the stability of microtubules (23). *In vitro* experiments performed by Csizmadia *et al.* showed that when proteasome inhibitors were present, proteins with erroneous folding accumulated, impairing cell function and leading to neurotoxicity (24). A study investigating the mechanism behind bortezomib-induced PN in rats found that rats treated with a combination of reduced glutathione showed neuropathological favorable changes compared to rats treated with saline. This confirmed that reactive oxygen species (ROS) release leads to CIPN production. Glutathione alleviated systemic toxicity in rats and reduced ROS release in neuronal cells, but did not reverse CIPN. A clinical study investigating the effect of glutathione on neurotoxicity, oxaliplatin pharmacokinetics, and platinum-deoxyribonucleic acid (Pt-DNA) adduct formation in 27

colorectal cancer patients treated with FOLFOX4 adjuvant therapy found that patients treated with glutathione showed significantly ( $P=0.0037$ ) lower than the placebo group between above contents; however, there were no significant differences in the pharmacokinetic parameters. Thus, this work shows that glutathione is an effective strategy for reducing oxaliplatin-induced PN without affecting the pharmacokinetics of oxaliplatin and the formation of Pt-DNA adducts (25). However, a double-blind, placebo-controlled trial of 185 patients treated with paclitaxel and carboplatin failed to show that glutathione was beneficial. As carboplatin is the least neurotoxic platinum drug, glutathione did not effectively prevent paclitaxel-induced PN (26). Further, the results of the North Central Cancer Treatment Group/Combined Trial n08ca did not support the use of glutathione in preventing paclitaxel/carboplatin-induced CIPN (14). In addition to glutathione, there is evidence that vitamins B3, B6, and B12 can protect patients from the occurrence, development or severity of CIPN (27). In a prospective, randomized, placebo-controlled trial, 71 patients underwent chemotherapy with paclitaxel, oxaliplatin or vincristine. The main results of this study showed that vitamin B did not significantly reduce the incidence of CIPN ( $P=0.22$ ), but did significantly improve sensory neuropathy perception ( $P=0.03$  at 12 weeks;  $P=0.005$  at 24 weeks;  $P=0.021$  at 32 weeks). Additionally, the risk estimates for sensory neuropathy perception were also statistically different at the time chemotherapy was stopped and after the 12-week follow-up period [odds ratio (OR): 5.78, 95% CI: 1.63–20.5, and OR: 8.1 at 32 weeks, 95% CI: 1.23–53.2] (28). In this study, we confirmed that glutathione combined with mecobalamin reduced the incidence of CIPN (31.6% *vs.* 47.7%), especially level 2 and level 3 CIPN ( $P=0.048$  and 0.040, respectively). Thus,



reduced glutathione combined with mecobalamin not only reduced the incidence of MM-related PN, but also reduced the severity of its occurrence.

Next, we analyzed PN as a dependent variable and found that patients with diabetes had a significantly higher incidence of PN ( $P=0.016$ ) and a more severe form of PN ( $P=0.032$ ). In study group, there was a higher incidence of grade 2–4 PN than grade 1 PN, and the difference in severity was statistically significant ( $P=0.010$ ). The logistic regression analysis revealed that MM patients with diabetes were 3.484 times more likely to develop PN than patients without diabetes. It is likely that diabetes increases the incidence of MM-related PN and aggravates neurological damage in patients (29).

In this study, the incidence of subcutaneously injecting bortezomib was 46%, which was significantly lower than that observed for an intravenous injection (54%). This difference was not statistically significant; however, the analysis confirmed that changing the route of administration affected the severity of PN ( $P=0.043$ ). A further analysis revealed that the incidence of grade 2 and higher PN in the subcutaneous injection group was significantly lower than grade 1 PN ( $P=0.008$ ). Moreau *et al.* confirmed that plasma exposure to bortezomib was similar for subcutaneous and intravenous injections as shown by two randomized studies of MMY-3021 and CAN-1004 in which the pharmacodynamics were comparable. In addition, bortezomib has been shown to reduce the overall incidence of grade 3 adverse events, especially the incidence of PN (30). The initial analysis of MMY-3021 was performed after the last patient completed 4 cycles of bortezomib treatment, with a median follow-up period of <1 year. Arnulf *et al.* reported the final survival analysis of the last patient after 1 year randomization (31). A significant decrease in the incidence of PN comparing subcutaneous and intravenous injections (all grades: 38% *vs.* 53%;  $P=0.044$ ; Level 2 and above: 24% *vs.* 41%;  $P=0.012$ ; Level 3 and above: 6% *vs.* 16%;  $P=0.026$ ) was also observed. Minarik *et al.* conducted a retrospective analysis of a randomized trial (32). The cohort included primary patients, patients treated with bortezomib regimens, and patients treated with autologous stem cell transplantation (ASCT). When comparing the two groups of patients receiving different types of bortezomib injection methods, no difference was found in the incidence of PN between the two groups. Specifically, the intravenous injection group had a 48% incidence of PN and the subcutaneous injection group had a 41% incidence of PN. The incidence of grade 2 PN in the

intravenous injection group compared to the subcutaneous injection group was 20% versus 18%, and the incidence of grade 3 PN in these groups was 6% *vs.* 4%. Conversely, the present analysis showed that the incidence of PN was dose-dependent and could be reduced by lowering the treatment intensity (to bortezomib once a week) rather than by the route of administration. Thus, additional research needs to be conducted to confirm the significance of subcutaneously injecting bortezomib in reducing the occurrence of PN.

We further explored whether reduced glutathione combined with mecobalamin reduced the incidence of CIPN in patients with diabetes or those administered bortezomib intravenously. The incidence of PN in both groups was decreased (the former was 45.8% *vs.* 72.7%, the latter was 39.0% *vs.* 61.1%); however, the differences were not statistically significant. Glutathione combined with mecobalamin may improve chemotherapy-related PN, but may not significantly improve PN caused by patients with diabetes or patients experiencing different modes of administration.

The prognostic factors of MM were also analyzed in this study. EMD mostly occurs when MM progresses or recurs, and is a sign of poor prognosis. MM patients with EMD have a significantly shorter survival time than who without EMD (33–35). The univariate analysis showed that the risk of death in EMD-positive patients was 2.373 times higher than that in EMD-negative (95% CI: 1.282–4.393), and the median OS was 23.4 *vs.* 52.3 months ( $P=0.006$ ), respectively. Presently, there is no clear plan for the treatment of MM patients with extramedullary infiltration, and there are few relevant reports on the evaluation of its treatment effects. We also found that the risk of death for patients with elevated LDH was 1.934 times higher than that of patients with normal LDH (95% CI: 1.179–3.173), and the median OS for both was 41.9 and 58.9 months, respectively ( $P=0.009$ ). Many studies have reported that an increase in LDH is related to the serum concentrations of  $\beta_2$ -microglobulin, creatinine, and thymidine kinase, which predicts the proliferation of myeloma cells, the occurrence of extramedullary lesions, and a shorter survival time (36,37). Some have pointed out that a 17p13 deletion is associated with LDH levels and a 17p13 deletion is associated with a high risk of a poor prognosis in MM patients. New drugs, such as lenalidomide and bortezomib, cannot overcome the adverse effects of TP53 gene deletions caused by 17p deletions on MM prognosis (38,39).

Multiple myeloma-associated antigen-1 (MMSA-1) is a recently discovered MM-associated antigen. A multivariate

Proportional hazards model analysis predicted that MMSA-1 and LDH levels are independently associated with poor PFS and OS in patients with myeloma (40). Chim *et al.* observed 77 Chinese myeloma patients eligible for transplantation who received continuous thalidomide maintenance therapy with ASCT. After 3 induction regimens (19 underwent a PAD regimen, 33 a VTD regimen, and 25 a staged treatment), the 5-year OS and PFS rates were 66.4% and 36.2%, respectively. The univariate analysis showed that elevated LDH, ISS stage III, high  $\beta_2$  microglobulin, and failure to obtain CR/near complete response (nCR) after ASCT were all risk factors affecting OS and EFS. The multivariate analysis revealed that elevated LDH and age were risk factors for a poor prognosis of OS, and elevated LDH is the only negative factor for EFS. Chim found that the risk of death in patients with elevated LDH was 4.289 times higher than that in patients with normal LDH levels (95% CI: 1.500–12.260) (41). Our study suggested that the mortality risk for elevated LDH was 1.934. The question of whether glutathione combined with mecobalamin alleviates CIPN and improves prognosis still needs to be investigated. The sample size used in this study is small and related reports are limited. Further validation needs to be performed with a larger sample size.

In this study, we can conclude glutathione combined with mecobalamin can treat CIPN, heighten patients' live quality and not affect chemotherapy effects. But our study have some limits, such as selection bias, heterogeneity in patient management and poor data quality. Our results provide direction and focus for prospective studies, which can verify the effect of glutathione plus mecobalamin treatment of CIPN.

## Conclusions

In this study, reduced glutathione combined with mecobalamin was used to treat MM-related PN, and was found to not only reduce the incidence of PN but also to reduce the severity of disease. It had no significant effect on disease remission, or the PFS or OS of patients. This drug combination also had a good safety profile. Diabetes and intravenously administered bortezomib increases the incidence and severity of CIPN. Additionally, if reduced glutathione is combined with mecobalamin, blood glucose levels need to be controlled and bortezomib needs to be subcutaneously injected to reduce the incidence and severity

of PN. In addition, this study showed that elevated EMD and LDH are independent prognostic factors of MM, and glutathione combined with mecobalamin improves patient prognosis.

## Acknowledgments

The authors would like to thank all the patients for their cooperation. We would also like to thank Medical Record Department, Henan Cancer Hospital for providing us with facilities and technical support.

*Funding:* This study was supported by grants from the National Natural Science Foundation of China (No. 81470287) and the Henan Outstanding Person Foundation (No. 184200510007).

## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://dx.doi.org/10.21037/apm-21-3313>

*Data Sharing Statement:* Available a <https://dx.doi.org/10.21037/apm-21-3313>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/apm-21-3313>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics board of Affiliated Cancer Hospital of Zhengzhou University (No. 2020021301). Informed consent was taken from all the patients.

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(English Language Editor: L. Huleatt)

**Cite this article as:** Huang H, Zhao M, Liu X, Song J, Liu L, Liu Y, Xiang P, Wang Y, Fang B. Glutathione combined with mecobalamin in the treatment of chemotherapy-induced peripheral neuropathy in multiple myeloma: a retrospective clinical study. *Ann Palliat Med* 2021;10(12):12335-12346. doi: 10.21037/apm-21-3313