Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2022; vol 9 (2) : 162–170

Original Article

Curcumin for Quality of Life of Multiple Myeloma Patients: a Randomized, Placebo-Controlled Trial

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v9i2.757

Accepted: June 21th, 2022
Approved: July 6th, 2022

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Abstract

Background : The main goal of multiple myeloma (MM) therapy is to control the disease, prolong the survival, and improve the life quality. Curcumin affects pro-inflammatory cytokines. There is no research yet that has been conducted to evaluate the effects of curcumin on increasing MM patient's life quality. Objective of this study is to evaluate the effect of curcumin on increasing MM patients' life quality.
Methods : Of 24 MM patients were enrolled and were divided randomly into treatment groups (n=12) and controls (n=12). Patients in treatment group received melphalan 4 mg/m^2, prednisone 40 mg/m^2 (MP) for 7 days and curcumin 8 grams/day for 28 days. The control group received MP and placebo. Quality of life (QoL) scores were measured in early diagnosis and after 4 cycles of treatment. The difference between two groups was analyzed using Mann-Whitney U-Test or Independent T Test.
Results : The role function score of the treatment group was better than control. There is a significant difference function score of patients between the treatment and control group, at baseline and 4 cycles treatment (41.66 ± 3.85 vs. 23.61 ± 3.36; 95.83 ± 1.03 vs 76.39 ± 2.51; *p*=0.022). There was significantly different of insomnia score between treatment and control goup at baseline and the end 4 cycles (41.67 ± 3.79 vs 58.33 ± 3.51; 9.72 ± 1.5 vs 25 ± 1.32; *p*=0.02).
Conclusion : The addition of curcumin in myeloma patients enhances the QoL score, role function score and lowered symptom insomnia.

Keywords : myeloma, curcumin, QoL scores, role function, symptom insomnia

INTRODUCTION

Multiple myeloma (MM) is a plasma cell malignancy that manifested heterogeneously and can affect tissues/organs.[1] MM covers 1% of all malignancies and 10% of hematologic malignancies. MM is the second most common hematologic malignancy after non-Hodgkin's lymphoma. Globally, it is estimated that there are 86.000 MM cases per year and approximately 63.000 MM patients are reported to die each year.[2] MM is still an incurable disease; the natural course of MM is characterized by a continuous risk of relapse, with each development being less responsive to therapy and each remission shorter than before.[3] The most complications of myeloma are renal insufficiency, hematological complications, infection, bone involvement, and neurological.[4,5] Optimal treatment of myeloma patients who ineligible transplant is an improving outcome and maintaining the quality of life.[6] The therapeutic goal of myeloma patients is to control the disease as an effort to prolong survival and improve quality of life. Patients with active MM were classified into the categories of Newly Diagnosed Multiple Myeloma (NDMM) stem cell transplant (SCT), NDMM which SCT could not do and relapsed and or refractory groups (RRMM). The approach to MM therapy is based on several factors such as age, comorbid disease, and performance status.[7,8]

One of the NDMM therapies for the ineligible transplant patient is melphalan-prednisone regiment.[9] Curcumin *(diferuloylmethane)* is a derivative of Curcuma longa which is safe to be used as an anti-tumor. There have been many studies of curcumin clinical trials in various cases, including colorectal cancer, pancreatic cancer, breast cancer, prostate cancer, lung cancer, head, and neck cancer. In MGUS (Monoclonal gammopathy indeterminant significant) curcumin reduces urine paraprotein and collagen type I N-telopeptide. Pleiotropic curcumin activity modulates several signaling molecules such as pro-inflammatory cytokines, apoptotic proteins, NF-kB, cyclooxygenase-2-5-LOX, STAT3, C-reactive protein, prostaglandin E2, prostate-specific antigens, adhesion molecules, phosphorylase kinase, transforming growth factor -b, ET-1, HO-1.[10–20] Golombick *et al*. reported the improvement in disease activity included serum free light chain, paraprotein, and percentage of bone marrow plasma cells, and no toxic effects in two male patients with Smoldering Multiple Myeloma who received oral curcumin for two years.[22] Abbas Zaidi *et al*. reported MM patients who started oral curcumin supplementation every day during the third relapse, without anti-myeloma treatment, patients plateaued and remained stable over the last 5 years with a good quality of life.[21]

Increasing survival of MM needs to be followed by understanding and measurement of health-related quality of life (HRQOL). Maintaining good HRQOL is one of important goal in taking care of MM patients. The final stage of organ damage is commonly seen in MM, along with treatment side effects which can affect all HRQOL domains, including physical symptoms such as fatigue and pain, worries about the future, changes in body image and impaired role function. Health quality instruments that are related to health can be attributed to clinical research, health economic evaluation, and clinical practice. Clinical application of HRQOL instruments included determining prognosis, monitoring the response to treatment, prioritizing problems, or facilitating communication.[23] Given the increasing MM incidence per year, there are still many cases of MM that have not been transplanted in Indonesia, most of the chemotherapy given to MM patients in Indonesia is melphalan-prednisone, it is necessary to conduct a study on the synergistic effects of curcumin by melphalan-prednisone on the quality of life of MM patients. Objective of this study is to evaluate the effect of curcumin on increasing MM patients' life quality.

METHODS

The clinical trial was conducted at RSUP Dr. Kariadi Semarang during February 2016 to May 2017. Estimate sample size is calculated by two sample situation. Subjects were simple blinding randomized into two groups; the treatment group which the patient were given MP regiment on days 1–7 and curcumin 8 grams/day on days 1–28. The control group was given MP regiment at days 1–7 and placebo on days 1–28. The dose of MP regiment was melphalan 4mg/m^2 and prednisone 40 mg/m^2. The treatment was carried out for four cycles. The baseline data of the research examined was age, creatinine clearance, hemoglobin, VAS score, initial QoL score, five initial function scores (physical, roles, emotions, cognitive, and social function), and nine initial symptom scores (fatigue, nausea, vomiting, pain, dyspnea, insomnia, decrease appetite, constipation, diarrhea, and financial difficulties). QoL scores, five function scores, and nine symptom scores were repeated in the fourth month.

Complete blood count was measured by flow cytometry method (Cell-Dyn Saphire; Abbott Diagnostics Division, Santa Clara, CA, USA). Serum creatinine (Cr) level was measured by the enzymatic method (TMS, Tokyo Boeki Machinery LTD, Japan). The quality of life scores in this study used the EORTC QLQ–C30 questionnaire that translated into Indonesian. The patients filled out the questionnaire accompanied by the author when they came for control.

The diagnosis of MM in this study is based on IMWG 2014 criteria, which are plasma clonal bone marrow ≥10% or discovery plasmacytoma on bone biopsy or organ extramedullary, and one or more of the following: a) evidence of organ damage: calcium >11

mg/dL , creatinine >2 mg/dL, Hb <10g/dL, ≥1 lytic lesion on bone radiography, CT, or PETCT, b) Biomarkers of malignancy : clonal plasma in the bone marrow ≥ 60% , ± serum involvement free light chain (FLC) ratio ≥100, >1 lesion on MRI .

Inclusion criteria were newly diagnosed multiple myeloma patients, age ≥ 18 years old, not eligible for bone marrow graft, willing to sign an informed consent. Exclusion criteria are sepsis or severe infection, pregnancy, patients with severe illness (such as hepatitis acute, chronic hepatitis, cirrhosis) or SGOT> 3x above the normal limit, subjects participated in other studies, ECOG IV.

Additional curcumin is the independent. Confounding variables are hemoglobin levels, creatinine clearance levels, VAS scores. Dependent variables are QoL score, role function score, insomnia score.

Ethical approval and consent

The study was approved by the Ethical Committee of the Faculty of Medicine, Diponegoro University and Dr. Kariadi Hospital (Ethical Number: 66/EC/FK/RSDK/2010). All subjects were given information regarding this study and signed the informed consent. This study was conducted in accordance with the Declaration of Helsinki.

Data analysis

Comparison mean of the data between two groups were analyzed using Independent T-Test if the data are normally distributed or using Mann-Whitney if the data are not normally distributed. These data were analyzed using IBM SPSS.

RESULTS

1. Demographics and characteristics of the study population

Demographic and basic characteristics of the study population between the two groups did not show any significant differences in variables: age, sex, creatinine

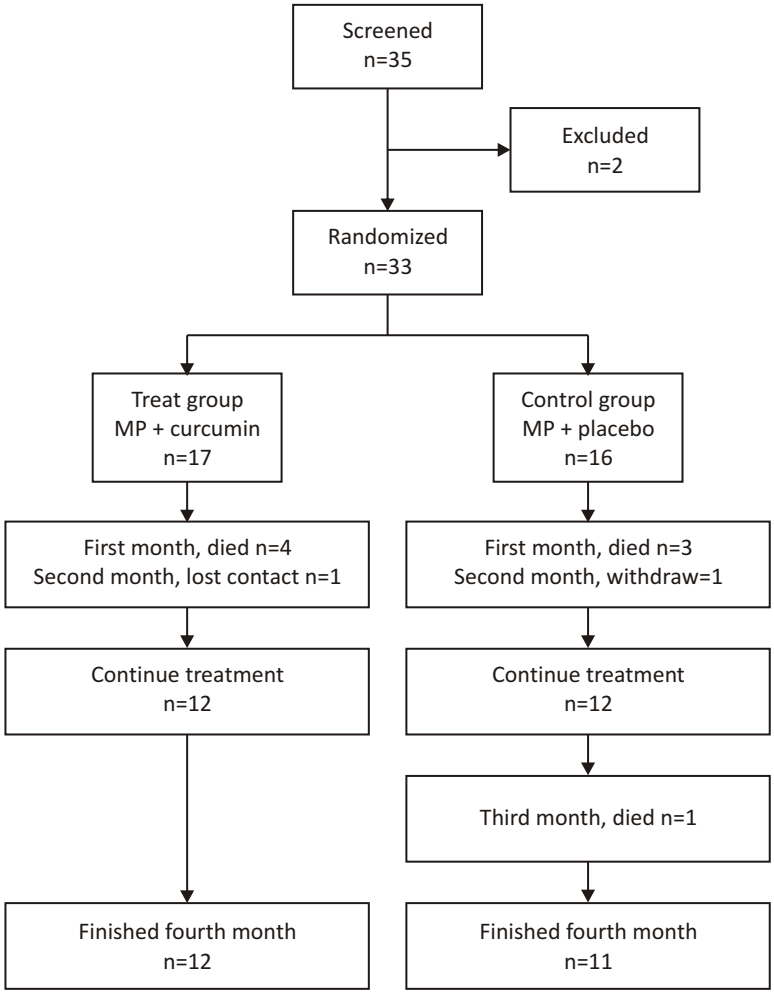

Figure 1. Consort study

TABLE 1
Basic characteristics of the study population

Characteristics	Treatment Group	Control Group
Subjects (n = 24)	12	12
Age		
Mean ± SD	54.92 ± 8.88	58.33 ± 10.11
Gender		
Man	8	6
Women	4	6
Creatinine clearance (ml/minute/1.73m^2, mean + SD)	47.91 ± 35.58	43.12 ± 20.05
Hemoglobin (g/dL, mean ± SD)	8.55 ± 2.24	8.87 ± 1.64
Initial QoL score		
Mean ± SD	55.55 ± 2.28	45.83 ± 1.44
VAS score		
Mean ± SD	6.5 ± 2.4	7.3 ± 1.5
Status Performance (ECOG)		
0	8 (66.67%)	4 (33.33%)
1	3 (25%)	4 (33.33%)
2	–	2 (16.67%)
3	1 (8.33%)	2 (16.67%)
Fracture		
Yes	3	4
Not	9	8
Bone lytic lesions		
Yes	10	12
Not	2	–
Recurrent infection		
Yes	3	2
Not	9	10
Durie–Salmon Stadium		
I	–	–
II	–	–
III	6	9
IV	6	3
ISS Stadium		
I	1	1
II	–	1
III	11	10

Characteristics	Treatment Group	Control Group
Initial physical function score		
Mean ± SD	53.33 ± 3.4	23.88 ± 3.08
Initial role function score		
Mean ± SD	41.66 ± 3.85	23.61 ± 3.36
Initial emotional function score		
Mean ± SD	62.49 ± 4.03	51.38 ± 3.36
Initial cognitive function score		
Mean ± SD	81.94 ± 2.18	76.38 ± 2.96
Initial social function score		
Mean ± SD	83.33 ± 2.75	72.22 ± 2.39
Initial fatigue score		
Mean ± SD	59.75 ± 3.39	65.72 ± 2.9
Initial nausea and vomiting score		
Mean ± SD	16.67 ± 2.56	33.33 ± 3.48
Initial pain score		
Mean ± SD	65.27 ± 3.58	83.33 ± 2.46
Initial dyspnea score		
Mean ± SD	25 ± 3.51	30.55 ± 3.32
Initial insomnia score		
Mean ± SD	41.67 ± 3.79	58.33 ± 3.51
Initial decreases of appetite score		
Mean ± SD	47.22 ± 3.61	47.22 ± 4.13
Initial constipation score		
Mean ± SD	22.22 ± 2.59	27.77 ± 3.71
Initial diarrhea score		
Mean ± SD	13.88 ± 2.22	16.67 ± 3.33
Initial financial difficulties score		
Mean ± SD	8.33 ± 1.5	19.44 ± 2.23
Level of education		
≥ Junior high school	6	5
< Junior high school	6	7

Remarks 1) Mann-Whitney, 2) Independent T-Test, 3) Chi-Square Test

clearance, hemoglobin level, VAS score, education level, baseline QoL score, performance status, fracture, bone lytic lesion, recurrent infection, stage, role functioning scores, emotional function, cognitive function, social function, and nine score symptom (Table 1).

2. The effect of adding curcumin to the QoL score

Increased QoL scores were obtained in the treatment and control groups. There were no significant differences in the QoL score between the treatment and control groups after observing the fourth month ($p = 0.214$). (Table 2)

TABLE 2
Effect of additional curcumin on QoL scores

Variable (month)		Mean ± SD	Delta	P
QoL Score (0)	Treatment	54.92 ± 8.88		0.21[1]
	Control	58,33 ± 10,11		
QoL Score (4)	Treatment	80.55 ± 1.39	25	
	Control	73.61 ± 8.57	27.77	

Remarks 1) Mann-Whitney U Test

TABLE 3
Effect of addition of curcumin on five function scores

Variable (month)	Mean ± SD		Delta		*P*
	Treatment	Control	Treatment	Control	
Physical function (0)	53,33 ± 3,4	23.88 + 3.08			
Physical function (4)	86.11 ± 1.46	82.22 + 1.56	33.89	58.33	0.55[1]
Role function (0)	41.66 ± 3.85	23.61 + 3.36			
Role function (4)	95.83 ± 1.03	76.39 + 2.51	54.16	52.78	0.02[1]
Emotional function (0)	62.49 ± 4.03	51.38 + 3.36			
Emotional function (4)	93.05 ± 1.16	51.38 + 3.36	30.56	34.72	0.28[1]
Cognitive function (0)	81.94 ± 2.18	76.38 + 2.96			
Cognitive function (4)	93.05 ± 8.58	84.72 + 2.18	11.11	8.33	0.48[1]
Social functions (0)	83,33 ± 2,75	72.22 + 2.39			
Social functions (4)	97.22 ± 6.48	91.67 + 2.07	13.88	19.44	0.86[1]

Remarks 1) Mann-Whitney U Test

3. The effect of adding curcumin to the five function scores

Increased five function scores were obtained in the treatment and control groups. There were no significant differences in physical, emotional, cognitive, and social function scores between the treatment and control groups after the fourth-month observation. There were significant differences in the role function scores between the treatment and control groups after observing the fourth month (Δ 54.16 vs 52.78; $p = 0.022$) (Table 3).

4. The effect of adding curcumin to nine score symptom

Decreased symptom insomnia score obtained in the treatment and control groups. There is a significant difference symptom insomnia scores between treatment and control groups (Δ-31.94 vs. -33.33; $p = 0.017$). Fatigue symptom scores, nausea, vomiting, pain, dyspnea, decreased appetite, constipation, diarrhea, and financial difficulties also declined in the two groups but did not differ significantly (Table 4).

DISCUSSION

This study reveals that there is a significant improvement in insomnia symptoms between patients in treatment groups and control groups. Symptom insomnia can be related to depression in patients with malignancy. Previous research found antidepressant curcumin activity through two mechanisms, hippocampal neurogenesis and inhibiting the monoamine oxidase enzyme, increasing brain serotonin, dopamine and noradrenaline levels. Sanmukhani *et al*. RCTs performed on 60 patients with the major depressive disorder for 6 weeks, found an increase in Hamilton's depression score in the group receiving 1000 mg of curcumin,

TABLE 4
Effect of addition of curcumin to nine scores symptom

Variable (month)	Mean ± SD		Delta		*P*
	Treatment	Control	Treatment	Control	
Fatigue score (0)	59.75 ± 3.39	65.72 ± 2.9			
Fatigue score (4)	12.03 ± 1.11	15.74 ± 1.67	-47.71	-49.98	0.73[1]
Nausea and vomiting score (0)	16.67 ± 2.56	33,33 ± 3,48			
Nausea and vomiting score (4)	2.78 ± 6.48	5.56 ± 1.08	-13,885	-27.77	0.57[1]
Pain score (0)	65.27 ± 3.58	83,33 ± 2,46			
Pain score (4)	15.28 ± 1.32	16.67 ± 1.88	-49.99	-66.66	0.93[1]
Dyspnea score (0)	25 ± 3.51	30.55 ± 3.32			
Dyspnea score (4)	11.11 ± 1.64	19.44 ± 1.71	-13.89	-11.11	0.23[1]
Insomnia score (0)	41.67 ± 3.79	58.33 ± 3.51			
Insomnia score (4)	9.72 ± 1.5	25 ± 1.32	-31.94	-33.33	0.02[1]
Decreases of appetite score (0)	47.22 ± 3.61	47.22 ± 4.13			
Decreases of appetite score (4)	8.33 ± 1.5	11.11 ± 1.64	-38.89	-36.11	0.66[1]
Constipation score (0)	22.22 ± 2.59	27.77 ± 3.71			
Constipation score (4)	0	5.56 ± 1.92	-22.22	-22.22	0.32[1]
Diarrhea score (0)	13.88 ± 2.22	16.67 ± 3.33			
Diarrhea score (4)	2.78 ± 9.62	2.78 ± 9.62	-11.11	-13.89	1[1]
Financial difficulties score (0)	8.33 ± 1.5	19.44 ± 2.23			
Financial difficulties score (4)	8.33 ± 1.5	11.11 ± 2.17	0	-8.33	0.91[1]

Remarks 1) Mann-Whitney U Test

fluoxetine 20 mg, and a combination of both, but not statistically significant.[24] Cancer-related insomnia adds to the burden of cancer symptoms and impacts on the quality of life of patients and their families/caregivers. Insomnia is associated with fatigue, pain, depression, and anxiety. Elderly and women may be more vulnerable. Insomnia worsens when cancer develops. If no immediate intervention will be a significant impact on the cost and use of the health care system, increase medical visits and hospitalizations. The pathophysiology of cancer-related insomnia is unknown. Cancer affects hormone levels and disrupts sleep homeostasis. Cytokines such as interleukin, interferon, and Tumor Necrosis Factor (released due to tumor growth) can activate the hypothalamic-pituitary-adrenal axis to release corticosteroid, including cortisol, which can interfere with normal sleep. In advanced cancer, people may be at higher risk for circadian function disorders.[25]

In this study, we found an increase in quality of life scores in the treatment and control groups. There have been no previous studies that assessed the quality of life of MM patients who received curcumin. Previously according to Waage in MM patients who received MPT and MP, obtained QoL score increased in the MPT and MP groups, symptom of constipation significantly more in the MPT group, diarrhea significantly more in the MP group, as well as significant differences in social functioning.[26] In contrast to Waage, role function scores in this study found significant differences between the treatment and control groups (p=0.022). The role function assesses the patient's ability to do work or household tasks, while the social function assesses whether the physical condition and treatment that are affected family life and social activities.[27] Increase in the quality of life score in this study is also inseparable from the administration of melphalan-prednisone. The MP regimen is the chosen regimen for MM patients who do not get a bone marrow transplant. Melphalan works as a cytotoxic agent, immunostimulant, inhibiting interleukin–6, and the immunogenic effect.[9] Maintaining a good quality of life in MM patients is important while the 5-year survival rate <40% and the median survival of

33 months.[28]

One of the side effects of curcumin supplementation is the gastrointestinal symptom. In this study, nausea, vomiting, and diarrhea in both groups experienced a decrease which did not differ statistically. This is in accordance with the dose of curcumin which can still be tolerated which is 8 g/day in pancreatic cancer cases even up to 18 months, there are no side effects, although the bioavailability of oral curcumin is not good.[15] Curcumin and its metabolites can be detected in plasma at doses >3.6 gr/day.[13]

There are several limitations to this study. In this study, an objective measurement of excretion of curcumin metabolites has not been carried out which illustrates the bioavailability of oral curcumin. In this study, we did not measure cortisol, serotonin, dopamine, noradrenaline levels related to insomnia and depression.

In the study, major and minor hypotheses were received. The addition of curcumin to MM patients provides a good therapeutic response, works synergistically with melphalan-prednisone, and is safe. This can be a consideration for the clinician to provide complementary therapy in MM management. Evaluation of quality of life needs to be done in MM patients considering the MM nature is incurable but can be controlled. Quality of life evaluation with the EORTC CLC-Q30 questionnaire is a questionnaire that is already widely used and practical.

The addition of curcumin in MM patients improved quality of life increased role function and reduced insomnia. Necessary to measure objectively curcumin metabolite excretion and levels of cortisol, serotonin, dopamine, noradrenaline, related to insomnia and depression. The addition of curcumin to MM patients provides a good therapeutic response, works synergistically with melphalan-prednisone, and it is safe. This can be a consideration for the clinician to provide complementary therapy in MM management.

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