

## **Effect of different therapeutic regimens on the elderly patients with multiple myeloma.**

**Hao Yang<sup>1</sup>, Liangsoo Yang<sup>2\*</sup>, Ling Wang<sup>1</sup>, Qi Pan<sup>1</sup>, Shuai Wang<sup>1</sup>**

<sup>1</sup>Department of 2<sup>nd</sup> Orthopedics, the people's Hospital of Zhumadian City, Henan Province, PR China

<sup>2</sup>Department of Orthopedics, Wuyang People's Hospital. Henan Province, PR China

### **Abstract**

**Objective:** To explore the effect of different therapeutic regimens on the patients with Multiple Myeloma (MM).

**Methods:** In Melphalan and Prednisone (MP) group, patients received 8 mg/m<sup>2</sup>/d melphalan and 60 mg/m<sup>2</sup>/d prednisone for 6 cycles (7 days each cycle). In M2 (VMBCP) group, patients received 1 mg/m<sup>2</sup>/d vincristine, 20 mg/m<sup>2</sup>/d carmustine and 400 mg/m<sup>2</sup>/d cyclophosphamide on Day 1, 8 mg/m<sup>2</sup>/d melphalan on Day 1-4, and 30 mg/m<sup>2</sup>/d prednisone on Day 1-14 for 6 cycles (14 days each cycle). In M2 and MP group, two regimens were applied alternately for 6 cycles. In Multiple CCT groups, multiple combination chemotherapy were adopted, including VMCP regimen (0.4 mg/m<sup>2</sup>/d vincristine and 100 mg/m<sup>2</sup>/d cyclophosphamide on Day 1, 8 mg/m<sup>2</sup>/d melphalan on Day 1-4 and 60 mg/m<sup>2</sup>/d prednisone Day 1-14), VBAP regimen (1 mg/m<sup>2</sup>/d vincristine and 75-100 mg/m<sup>2</sup>/d carmustine on Day 1, 30 mg/m<sup>2</sup>/d doxorubicin and 60 mg/m<sup>2</sup>/d prednisone on Day 1-4), VAD regimen (0.4 mg/m<sup>2</sup>/d vincristine on Day 1-4 with infusion for 24 h, 40 mg/m<sup>2</sup>/d dexamethasone on Day 1-4, 9-12 and 1720), CVP regimen (100 mg/m<sup>2</sup>/d cyclophosphamide and 0.4 mg/m<sup>2</sup>/d vincristine on Day 1-4, 60 mg/m<sup>2</sup>/d prednisone on Day 1-14) and ECP regimen (100 mg/m<sup>2</sup>/d etoposide on Day 3-5, 100 mg/m<sup>2</sup>/d cyclophosphamide and 60 mg/m<sup>2</sup>/d prednisone on Day 1-5). Response rate and survival time of different groups are compared.

**Results:** The total response rate of 100 patients treated with conventional chemotherapy was 46.0%, and complete response rate and partial response rate were 15.0% and 31.0%, respectively. The total response rate of patients treated with combination chemotherapy was significantly higher than that of patients treated with melphalan and prednisone (59.1% vs. 29.2%, t=38.456, P<0.05). The median survival time, 3 and 5 year overall survival of 108 MM patients were 31.0 months, 33.0% and 16.1%, respectively.

**Conclusions:** Combination chemotherapy could be used for the patients with multiple myeloma.

**Keywords:** Multiple myeloma, Therapeutic regimen, Therapeutic effect.

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### **Introduction**

Multiple Myeloma (MM) is a systematic malignant neoplastic hematologic disorder caused by abnormal cloned proliferation of plasma cells. As a disease difficult to cure in clinical, it accounts for 10% of hematologic malignant. MM is characterized by a clonal proliferation of plasma cells that produces monoclonal immunoglobulin or monoclonal protein (M protein) [1]. Meanwhile, decrease of normal immunoglobulin causes further damage in tissues and organs [2,3]. Multiple myeloma is occurring with increasing frequency in older patients (age>60) and male patients is more than female patients. Without timely treatment, the median survival time of MM patients in progressive stage is only 6-12 months [4]. Characteristic clinical symptoms of multiple myeloma include anaemia, infection, osteodynia, osseous damage and kidney damage, finally influencing individual life

quality. Currently, older patients with multiple myeloma have traditionally received an oral regimen combining Melphalan and Prednisone (MP) [5]. Although this treatment can improve survival time of patients, it easily leads to high tolerance and recurrence rate [6,7]. So new treatments are needed. In this study, 108 MM patients treated in our hospital from January 1, 2005 to December 31, 2015 were selected and their treatment records and follow-up visit were analysed in order to compare efficacy of different therapeutic regimens and provide scientific basis for clinical guideline of MM.

### **Data and Methods**

#### **General data**

Based on Standard of Diagnosis and Curative Effect of Hematopathy edited by Zhang, 108 MM patients treated in our

hospital from January 1, 2005 to December 31, 2015 were selected, among which male patients accounted for 71.3% (n=77) and female patients 28.7% (n=31) with mean age  $67.4 \pm 0.6$  [8]. In clinical classification, IgG type accounted for 45.4% (n=49), IgA type 24.1% (n=26), IgD type 4.6% (n=5), none secretion type 2.8% (n=3), light chain type 21.3% (n=23) and biclonal type 1.8% (n=2). According to Durie-Salmon staging system in preliminary diagnosis, stage I accounted for 3.7% (n=4), stage II 12.0% (n=13) and stage III 84.3% (n=91).

### Therapeutic regimens and grouping

Patients were divided into different treatment groups based on their medication.

In Melphalan and Prednisone (MP) group, patients received 8 mg/m<sup>2</sup>/d melphalan (GlaxoSmithKline, UK) and 60 mg/m<sup>2</sup>/d prednisone (Zhejiang Ju pharmaceutical co., LTD, China) for 6 cycles (7 days each cycle).

In M2 (VMBCP) group, patients received 1 mg/m<sup>2</sup>/d vincristine (Zhejiang Ju pharmaceutical co., LTD, China), 20 mg/m<sup>2</sup>/d carmustine (Zhejiang Ju pharmaceutical co., LTD, China) and 400 mg/m<sup>2</sup>/d cyclophosphamide (Zhejiang Ju pharmaceutical co., LTD, China) on Day 1, 8 mg/m<sup>2</sup>/d melphalan (Zhejiang Ju pharmaceutical co., LTD, China) on Day 1-4, and 30 mg/m<sup>2</sup>/d prednisone (Zhejiang Ju pharmaceutical co., LTD, China) on Day 1-14 for 6 cycles (14 days each cycle).

In M2 and MP group, two regimens were applied alternately for 6 cycles.

In Multiple CCT groups, multiple combination chemotherapy were adopted, including VMCP regimen (0.4 mg/m<sup>2</sup>/d vincristine and 100 mg/m<sup>2</sup>/d cyclophosphamide on Day 1, 8 mg/m<sup>2</sup>/d melphalan on Day 1-4 and 60 mg/m<sup>2</sup>/d prednisone Day 1-14), VBAP regimen (1 mg/m<sup>2</sup>/d vincristine and 75-100 mg/m<sup>2</sup>/d carmustine on Day 1, 30 mg/m<sup>2</sup>/d doxorubicin and 60 mg/m<sup>2</sup>/d prednisone on Day 1-4), VAD regimen (0.4 mg/m<sup>2</sup>/d

vincristine on Day 1-4 with infusion for 24 h, 40 mg/m<sup>2</sup>/d dexamethasone on Day 1-4, 9-12 and 1720), CVP regimen (100 mg/m<sup>2</sup>/d cyclophosphamide and 0.4 mg/m<sup>2</sup>/d vincristine on Day 1-4, 60 mg/m<sup>2</sup>/d prednisone on Day 1-14) and ECP regimen (100 mg/m<sup>2</sup>/d etoposide on Day 3-5, 100 mg/m<sup>2</sup>/d cyclophosphamide and 60 mg/m<sup>2</sup>/d prednisone on Day 1-5). The research ethics committee approval number is 200412050027.

### Effect evaluation and follow-up

Criterion of therapeutical effect was established by Standard of Diagnosis and Curative Effect of Hematopathy edited by Zhang [8]. The follow-up of patients continued from diagnose date to December 12, 2013.

### Statistical analysis

SPSS17.0 software was applied for data processing and statistical analysis. Based on survival curve, survival analysis was performed by Kaplan-Meier method, survival rate comparison by Log-rank test, and clinical features and response rate by  $\chi^2$  test. All methods used two-sided test with significant difference of  $P < 0.05$ .

## Results

### Clinical data of patients

Among 108 patients, 24 patients (22.2%) were treated with MP regimen, 29 patients (26.9%) were treated with M2 regimen, 22 patients (20.4%) with alternating MP and M2 regimen, 25 patients (23.1%) with multiple combination chemotherapy such as VMCP, VBAP, VAD, ECP, MP, M2 and VCP. Besides, 8 patients (7.4%) were administrated single thalidomide. Table 1 shows the main clinical features of patients in different chemotherapy regimens.

**Table 1.** Main clinical features of patients in different chemotherapy regimens.

Groups	Total number	Median age	Gender		Classifications					Stages		
			Male	Female	IgG	IgA	IgD	Light chain	Other	I	II	III
MP group	24	64	15	9	13	5	1	4	1	1	3	20
M2 group	29	61	21	8	12	8	2	5	2	1	5	23
MP+M2 group	22	69	16	6	11	4	1	5	1	1	2	19
Multiple CCT groups	25	65	19	6	11	6	1	6	1	1	1	23

### Therapeutic effect analysis of patients treated with chemotherapy

The total response rate of 100 patients in chemotherapy group was 46.0% (n=46) with CR rate of 15.0% (n=15) and PR rate of 31.0% (n=31). The total response rate of 24 patients in MP group was 29.2% with CR rate of 4.2% (n=1), PR rate of 25.0% (n=6) and none response rate of 37.5% (n=9). The total

response rate of 29 patients in M2 group was 41.1% with CR rate of 13.8% (n=4), PR rate of 27.6% (n=8) and none response rate of 24.1% (n=7). The total response rate of 22 patients in MP+M2 group was 59.1% with CR rate of 22.7% (n=5), PR rate of 36.4% (n=8) and none response rate of 18.2% (n=4), which is the highest among all groups (Table 2). The total response rate of 25 patients in Multiple CCT group was 56.0%

with CR rate of 20.0% (n=5), PR rate of 36.0% (n=9) and none response rate of 20.0% (n=5).

**Table 2.** Therapeutic effect analysis of 100 patients.

Groups	Total number	Therapeutic effect and patient number					Median survival time (month) (range)
		CR (%)	PR (%)	Progress (%)	None response (%)	Total response (%)	
MP group	24	1 (4.2)	6 (25.0)	8 (33.3)	9 (37.5)	29.2	30.5 (8~110)
M2 group	29	4 (13.8)*	8 (27.6)	10 (34.5)	7 (24.1)	41.4*	26.5 (8~120)*
MP+M2 group	22	5 (22.7)#	8 (36.4)	5 (22.7)	4 (18.2)	59.1#	40.5 (9~104)*
Multiple CCT group	25	5 (20.0)#	9 (36.0)	6 (24.0)	5 (20.0)	56.0#	28.5 (6~91)*

Compared with MP group: #P<0.05, \*P>0.05.

### Analysis of median survival time and survival rate

108 patients have a median survival time of 31 (6~110) months with mean value of  $39.6 \pm 2.3$  months. There is no significant difference ( $P>0.05$ ) of median survival times between MP group (30.5 months, 8~110) and CCT group (30 months, 9~77). Additionally, compared with MP group, median survival times have no significant difference ( $P>0.05$ ) in M2 group (26.5 months, 8~120), MP+M2 group (40.5 months, 9~104) and multiple combination chemotherapy group (28.5 months, 6~91), while MP+M2 group has a better result than M2 group ( $P<0.05$ ).

3-year and 5-year survival rate of 108 patients are 33.0% and 16.1%, respectively. Specifically, the rates in MP group are 21.4% and 12.8%. In M2 group, the rates are 30.8% and 11.1%, MP+M2 group 47.2% and 21.4%, and multiple combination chemotherapy group 27.8% and 22.9%. Groups above have no significant difference ( $P>0.05$ ).

### Discussion

Multiple Myeloma (MM) is occurring with increasing frequency in older patients [9]. Its incidence ranks behind only non-Hodgkin's lymphoma among haematological malignant tumor, seriously affecting lifetime and health of patients [10]. Currently, chemotherapy regimen and hematopoietic stem cell transplantation are the main treatment for MM. In our study, MP+M2 regimen obtains a significantly better result than MP regimen, and the survival time and survival rate of patients are also higher than the MP regimen. Although hematopoietic stem cell transplantation has less pain and good prognosis for patients with age<60, corresponding patient cases in the age range limits its application. The fact that most MM patients are the aged indicates high operative risk and unsatisfactory prognosis. Therefore, chemotherapy regimen is appropriate for elderly MM patients. As the common treatment for MM, chemotherapy drug combination is applied for better therapeutic effect. For example, VDT (bortezomib, dexamethasone and thalidomide) regimen is used for refractory or recurrent MM, leading to a total respond rate of 86.11% [11]. Besides, azole phosphonic acid injection is also applied

for spine MM, which effectively reduces pain in patients and has significant efficacy [12].

Briefly, along with the development of science, more effective and rational drugs and regimens with less side effects will be applied in clinical for MM patients. Finally, the lifetime of MM patients will be lengthened and quality of life improved.

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**\*Correspondence to**

Liangsuo Yang  
Department of Orthopedics  
Wuyang People's Hospital  
Henan Province  
PR China