Multi-drug Combination Therapy with Vincristine-Melphalan-Cyclophosphamide-Prednisolone Was More Effective than Cyclophosphamide-Prednisolone in Stage III Myeloma

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A cooperative randomized clinical trial to compare the effectiveness of multi-drug combination chemotherapy (VMCP, vincristine-melphalan-cyclophosphamide-prednisolone) with CP (cyclophosphamide-prednisolone) for the treatment of multiple myeloma was performed. When the whole group of patients was evaluated, the choice of chemotherapy (VMCP or CP) was not a significant prognostic factor associated with response or survival by uni- or multivariate analysis, and the difference between the survival curves of the treatment groups was only marginally significant. However, when the analysis was confined to stage III patients, the choice of chemotherapy became a significant prognostic factor associated with both response rate and survival, and the statistical difference between survival curves was significant. Taking the disease characteristics of multiple myeloma into consideration, the better result obtained with multi-drug combination chemotherapy in the treatment of stage III patients is consistent with other studies supporting the superiority of multi-drug combination chemotherapy for patients with overt systemic disease.

Key words: Multiple myeloma — Multi-drug combination chemotherapy — Standard chemotherapy — Multivariate analyses — Prognostic factors

Patients with multiple myeloma are seen only infrequently in most hospitals in Japan, and accordingly, the treatment of each patient is apt to be determined by the attending physician. At present, the most widely employed regimen for the treatment of myeloma is a combination of melphalan and prednisolone (MP).[1]

Western researchers have studied the efficacy of multi-drug combination chemotherapy since 1979.[2-9] However, whether or not multi-drug protocols are superior to standard MP remains controversial.[10] Turning to Japan, because of the low incidence of multiple myeloma, no systematic randomized clinical trials to evaluate multi-drug combination chemotherapy for its treatment have been reported.

The present study is a cooperative randomized clinical trial to compare the effectiveness of multi-drug combination chemotherapy as the primary therapy with that of a cyclophosphamide and prednisolone regimen, which is considered equivalent to the standard MP regimen.[11, 12]

PATIENTS AND METHODS

Patients studied Eighty-eight patients satisfying the diagnostic criteria for multiple myeloma proposed by the SWOG[13] in 12 different institutions located in central Japan between September 1983 and April 1987 were registered at the central office of the Nagoya Myeloma Cooperative Study Group located in Anjo Hospital. Patients eligible must have had no prior chemotherapy and had to have measurable serum or urinary M-protein. Patients were also required to have no other serious concurrent illness unrelated to myeloma. Each member was recommended to register only the patients with overt progressive disease. Nevertheless, it is still possible that some patients with indolent or smoldering myeloma were inadvertently included in the present trial.

The 88 patients were randomly assigned to one of two different drug combinations by telephone contact with the central office. The randomization was blocked and stratified on the basis of clinical stage (I+II vs. III) and serum creatinine level (≥ 2.0 vs. < 2.0 mg/dl).

Treatment regimens The two regimens consisted of vincristine - melphalan - cyclophosphamide - prednisolone

Table I. Chemotherapy Dose Regimens

VMCP	Vincristine	1 mg/m^2, d 1 iv
	Melphalan	4 mg/m^2, d 1–4 po
	Cyclophosphamide	100 mg/m^2, d 1–4 po
	Prednisolone	30 mg/m^2, d 1–4, po
CP	Cyclophosphamide	333 mg/m^2, d 1, 8, 15, 22 iv
	Prednisolone	30 mg/m^2, d 1–5, 15–19 po
	Prednisolone	7 mg/m^2, d 6–14, 20–28 po

Table II. Characteristics of Patients

Characteristic	VMCP (n=44)	CP (n=39)
Age		
≥65 years	20	18
<65 years	24	21
Sex		
male	27	20
female	17	19
M-protein type		
kappa	28	23
lambda	16	16
Stage		
I+II	17	17
III	27	22
Serum creatinine		
≥2.0 mg/dl	7	6
<2.0 mg/dl	37	33
Performance status		
0–1	19	16
≥2	23	23
Hemoglobin		
≥8.5 g/dl	24	26
<8.5 g/dl	18	12 .
Calcium		
≥11.5 mg/dl	3	1
<11.5 mg/dl	36	34
BUN		
≥30 mg/dl	6	5
<30 mg/dl	35	28
Albumin		
≥3.5 g/dl	25	26
<3.5 g/dl	17	13
Platelet		
≥100,000/mm^3	38	39
<100,000/mm^3	4	0

The difference in the distribution of the identified prognostic factors between the VMCP and CP treatment groups was not statistically significant as evaluated by Fisher's exact test.

(VMCP) or cyclophosphamide-prednisolone (CP), with dose schedules as shown in Table I. VMCP was repeated at 20-day intervals and CP was given weekly, provided there was recovery of leukocytes to more than 3,000/mm^3 and of platelets to more than 100,000/mm,^{3} until the serum and/or urine concentration of M-protein stopped decreasing.

Forty-five patients were randomized to receive VMCP (3 IA, 14 IIA, 21 IIIA and 7 IIIB) and the remaining 43 received CP (3 IA, 11 IIA, 3 IIB, 22 IIIA and 4 IIIB). At the time of analysis, 2 patients were found to be ineligible and 3 others were unevaluable (treatment refusal, hemodialysis during chemotherapy and protocol violation), leaving 83 patients evaluable. Although there were 3 patients who had been lost to follow-up at 2, 5, and 6 months, respectively, they were included in the analysis as censored cases.

Clinical response was evaluated based on the criteria proposed by the Chronic Leukemia-Myeloma Task Force.[14] Patients who showed a greater than 50% reduction in pretreatment serum and/or urine M-protein concentration for at least 4 weeks were designated as being in partial remission (PR). All patients who did not achieve PR were considered as treatment failures.

Remission maintenance Patients who showed no further reduction in M-protein after achieving PR were given remission maintenance therapy for 2 years. The remission maintenance regimen was the same regimen that had been employed in the remission induction, but was given at longer intervals. Patients rated as failures to CP or who relapsed after achieving PR on CP were treated with VMCP. Salvage therapy for patients rated as failures to VMCP or who relapsed after achieving PR on VMCP was not specified.

Prognostic factors The factors evaluated prior to treatment as potentially having prognostic significance included age, sex, M-protein type, clinical stage as defined by Durie and Salmon,[15] serum creatinine concentration, performance status, hemoglobin concentration, serum calcium concentration, BUN (blood urea nitrogen), serum albumin concentration, and platelet count (Table II).

Statistical methods Multiple statistical analyses were performed at the Department of Preventive Medicine, Nagoya University School of Medicine. Univariate analysis of the unadjusted association of each prognostic factor with the chemotherapeutic regimens was performed using Fisher's exact test for 2×2 contingency tables.[16] Uni- and multivariate analyses of the association of pretreatment prognostic factors with response were performed with the use of logistic regression

analysis[16] according to the LOGIST procedure[17] on the SAS program (Cary, NC).[18]

Survival was calculated from the date of the start of chemotherapy to the last follow-up date or death. Survival curves were constructed according to the Kaplan-Meier method.[19] The generalized Wilcoxon test[20] and logrank test[21] were used to assess the significance of the unadjusted difference in survival. Uni- and multivariate analyses were performed by the Cox proportional hazards model[22] according to the PHGLM procedure[23] on the SAS program[18] to identify subsets of independent prognostic factors for survival. Prognostic factors significant at the 0.05 level in the stepwise Cox proportional hazards model analysis were selected as the important ones influencing survival.

RESULTS

The difference in the distribution of the identified prognostic factors between the VMCP and CP treatment groups was analyzed by Fisher's exact test,[16] and no significant difference was observed (Table II).

Table III. Response to Chemotherapy in Relation to Patients' Characteristics

Prognostic factor	No.	PR rate (%)	Univariate P value	Multivariate[a] (81 cases)	
				P value	Beta
Chemotherapy					
VMCP	44	52.3			
CP	39	38.5	0.2091		
Age					
≥65	38	39.5			
<65	45	51.1	0.2902		
Sex					
male	47	38.3			
female	36	55.6	0.1198		
M-protein type					
kappa	51	41.2			
lambda	32	53.1	0.2889		
Stage					
I + II	34	55.9			
III	49	38.8	0.1260		
Serum creatinine					
≥2.0 mg/dl	13	38.5			
<2.0 mg/dl	70	47.1	0.5652		
Performance status					
0–1	35	55.6			
≥2	46	34.8	0.0468	0.0468	0.9163
Hemoglobin					
≥8.5 g/dl	50	50.0			
<8.5 g/dl	30	36.7	0.2477		
Calcium					
≥11.5 mg/dl	4	50.0			
<11.5 mg/dl	70	48.6	0.8673		
BUN					
≥30 mg/dl	11	45.5			
<30 mg/dl	63	46.0	0.9717		
Albumin					
≥3.5 g/dl	41	58.5			
<3.5 g/dl	30	40.0	0.5374		

a) In this analysis, four factors (hemoglobin, calcium, BUN and albumin) were excluded.

Prognostic factors for the PR rate to chemotherapy
Thirty-eight (46.5%) of the 83 patients treated with VMCP and CP achieved PR. Of 44 patients treated with VMCP, 23 (52.3%) achieved PR, as did 15 (38.5%) of 39 treated with CP. However, this difference between the PR rate in VMCP and CP was not statistically significant (Table III). Table III also includes eleven other clinical factors, determined at the time of diagnosis, which were evaluated individually as possible prognostic factors. Statistically significant ($P<0.05$) factors associated with response by univariate analysis were identified by performance status alone. These clinical factors were further evaluated in a stepwise logistic regression analysis. The analysis had to be restricted to 71 patients because data on at least one clinical factor in the univariate analysis

was unavailable in the remaining 12 patients. In this analysis, performance status lost its statistical significance, and no other clinical factor showed a statistically significant association with response. However, if the analysis was confined to seven factors (chemotherapy, age, sex, M-protein type, clinical stage, serum creatinine concentration, and performance status), complete data of which were available in 81 patients, performance status retained its significance (Table III).

Seven out of 24 patients rated as failures to CP were salvaged with VMCP, but only 3 achieved PR (42.9%). **Prognostic factors for survival** Survival curves for patients treated with VMCP and CP are shown in Fig. 1. The estimated 5-year survival rate for the 44 patients treated with VMCP was 34%, with a median survival of 30.5 months, while that for the 39 patients treated with CP was 27%, with a median survival of 15.9 months. This difference achieved marginal statistical significance by the generalized Wilcoxon test ($P=0.052$) but not by the logrank test ($P=0.186$). At the time of analysis, 20 patients (45.5%) treated with VMCP and 14 (35.9%) treated with CP, including 3 salvaged by VMCP, were alive.

The clinical factors evaluated for their predictive value of response were assessed for their relationship to survival. Three factors, clinical stage, serum creatinine concentration, and performance status were found to affect survival adversely by univariate analysis (Table IV).

These factors were evaluated further by the stepwise Cox proportional hazards model. Regardless of whether the analysis was performed on the 71 patients for whom all clinical data were available or on 81 for whom only 7 factors were available, only clinical stage retained its significance (Table IV).

Prognostic factors for PR rate to chemotherapy in stage III patients As the next step, we confined the evaluation
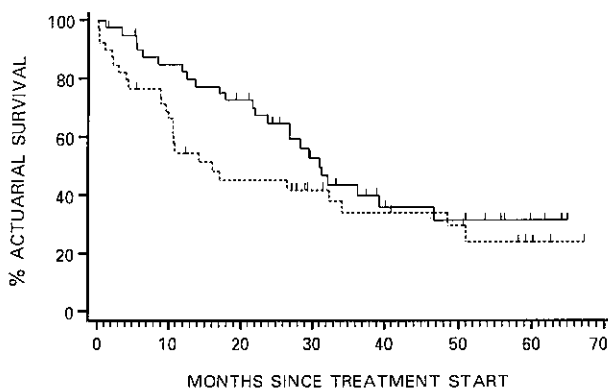

Fig. 1. Survival curves for patients treated with VMCP (solid line) or CP (broken line). The tick marks indicate patients alive at that interval. The difference between the curves was marginally significant by the generalized Wilcoxon test ($P=0.052$) but not by the logrank test ($P=0.186$).

Table IV. Cox Proportional Hazards Model Analysis of Survival

Prognostic factor		Univariate P value	Multivariate	
			P value	Beta
Chemotherapy	(VMCP/CP)	0.1892		
Age	($\geq 65/<65$)	0.7988		
Sex	(male/female)	0.2361		
M-protein type	(kappa/lambda)	0.4416		
Stage	(I+II/III)	0.0151	0.0230	0.7106
Serum creatinine (mg/dl)	($\geq 2.0/<2.0$)	0.0297		
Performance status	($0-1/\geq 2$)	0.0266		
Hemoglobin (g/dl)	($\geq 8.5/<8.5$)	0.0639		
Calcium (mg/dl)	($\geq 11.5/<11.5$)	0.2716		
BUN (mg/dl)	($\geq 30/<30$)	0.4399		
Albumin (g/dl)	($\geq 3.5/<3.5$)	0.9960		

Table V. Response to Chemotherapy of Stage III Patients

Prognostic factor	No.	PR rate (%)	Univariate P value	Multivariate[a] P value	Beta
Chemotherapy					
VMCP	27	51.9			
CP	22	22.7	0.0420	0.0337	1.5220
Age					
≥65	24	37.5			
<65	25	40.0	0.8575		
Sex					
male	26	30.8			
female	23	47.8	0.2242		
M-protein type					
kappa	29	27.6			
lambda	20	55.0	0.0568	0.0233	−1.5823
Serum creatinine					
≥2.0 mg/dl	10	40.0			
<2.0 mg/dl	39	38.5	0.9290		
Performance status					
0-1	15	46.7			
≥2	33	33.3	0.3788		
Hemoglobin					
≥8.5 g/dl	18	38.9			
<8.5 g/dl	29	37.9	0.9476		
Calcium					
≥11.5 mg/dl	3	33.3			
<11.5 mg/dl	41	41.5	0.8203		
BUN					
≥30 mg/dl	8	25.0			
<30 mg/dl	38	42.1	0.3754		
Albumin					
≥3.5 g/dl	31	41.9			
<3.5 g/dl	17	29.4	0.3937		

a) In this analysis, four factors (hemoglobin, calcium, BUN and albumin) were excluded.

to only those patients with advanced (stage III) disease. Forty-nine (59%) out of 83 patients had stage III disease. Of the 49 patients, 27 were treated with VMCP and 22 were treated with CP. Nineteen (38.8%) of the 49 stage III patients achieved PR. Fourteen (51.9%) of the 27 patients treated with VMCP and 5 (22.7%) of 22 treated with CP achieved PR.

Ten clinical factors were evaluated individually as possible prognostic factors. Importantly, when the study was confined to the patients with stage III disease, the choice of chemotherapy (VMCP or CP) became a statistically significant factor associated with response by univariate analysis. These factors were evaluated further in a stepwise logistic regression analysis. When the analysis was performed on 43 patients for whom data for all clinical factors were available, no variables met the 0.05 significance level. However, when the analysis was confined to six factors (age, sex, M-protein type, serum creatinine concentration, chemotherapy, and performance status), data of which were available in 48 patients, M-protein type and the choice of chemotherapy (VMCP or CP) were found to affect PR rate significantly (Table V).

Turning to stage I+II patients, 10 (58.8%) of the 17 patients treated with CP and 9 (52.9%) of 17 treated with VMCP achieved PR.

Prognostic factors for survival in stage III patients Survival curves for stage III patients treated with VMCP and CP are shown in Fig. 2. The estimated 5-year sur-

vival rate for the 27 patients treated with VMCP was 29%, with a median survival of 30.2 months, while that for the 22 patients treated with CP was 10%, with a median survival of 10.5 months. The difference between the two curves was statistically significant by both the generalized Wilcoxon test (P=0.015) and the logrank test (P=0.036). At the time of study, 11 stage III patients (40.7%) treated with VMCP and 5 (22.7%) treated with CP including 1 salvaged by VMCP were alive.

The clinical factors of stage III patients evaluated for predictive value for response were assessed for their relationship to survival. Only the choice of chemotherapy (VMCP or CP) was found to have a statistically significant correlation with survival by univariate analysis (Table VI).

These factors were examined further by a stepwise Cox proportional hazards model analysis. Regardless of

whether the analysis was performed on the 43 patients for whom data on all clinical factors were available or on the 48 for whom data on only six factors were available, the choice of chemotherapy retained its significance.

Turning to stage I + II patients, the estimated 5-year survival rate for the 17 patients treated with VMCP was 45%, with a median survival of 25.6 months, and that for the 17 patients treated with CP was 49%, with a median survival of 28.2 months. The difference between the survival curves for stage I + II patients treated with VMCP and CP was not statistically significant.

Toxicity Toxicity in patients of both treatment groups generally was mild. The median white blood cell count nadir was 2,800/mm^3 on day 17 in patients treated with VMCP and required 3 weeks to recover, in contrast to negligible leukocytopenia in patients treated with CP. Thrombocytopenia ($<$100,000/mm^3) was seen in 5 patients (11.4%) treated with VMCP, including 2 instances in which it was present before chemotherapy, and in 3 patients (7.7%) treated with CP. Infections occurred in 10–20% of patients in both treatment groups, but none were life-threatening. Gastrointestinal symptoms developed in 10%, and a slight, transient increase in the serum GPT concentration was noted in 15% of patients.

DISCUSSION

The effectiveness of multi-drug combination chemotherapy as a primary therapy for remission induction for the treatment of multiple myeloma has not been well established.[10] In comparison to the standard melphalan and prednisolone (MP) regimen,[1] only a minority of researchers have claimed that multi-drug combination chemotherapy is superior in terms of response rate and survival.[6, 24] In Japan, the situation is even less clear because of the limited number of patients as well as the lack of prospective randomized clinical trials.
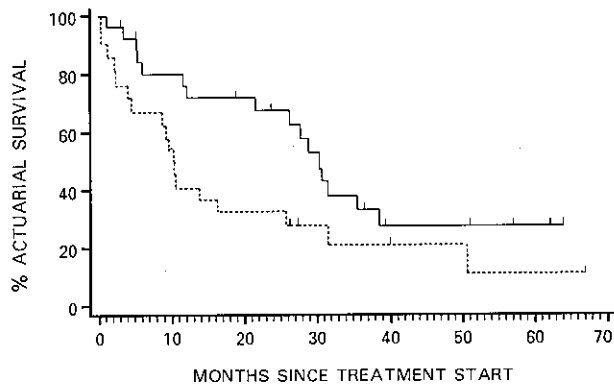

Fig. 2. Survival curves for stage III patients treated with VMCP (solid line) or CP (broken line). The difference between the curves was significant by both the generalized Wilcoxon test (P=0.015) and the logrank test (P=0.036).

Table VI. Cox Proportional Hazards Model Analysis of Survival for Stage III Patients

Prognostic factor		Univariate P value	Multivariate	
			P value	Beta
Chemotherapy	(VMCP/CP)	0.0403	0.0209	0.8720
Age	($\geq$65/$<$65)	0.6407		
Sex	(male/female)	0.4396		
M-protein type	(kappa/lambda)	0.3533		
Serum creatinine (mg/dl)	($\geq$2.0/$<$2.0)	0.2199		
Performance status	(0–1/$\geq$2)	0.1188		
Hemoglobin (g/dl)	($\geq$8.5/$<$8.5)	0.9360		
Calcium (mg/dl)	($\geq$11.5/$<$11.5)	0.1956		
BUN (mg/dl)	($\geq$30/$<$30)	0.2923		
Albumin (g/dl)	($\geq$3.5/$<$3.5)	0.5565		

In the present study, we conducted a cooperative randomized clinical trial to compare the effectiveness of multi-drug combination chemotherapy (VMCP, vincristine-melphalan-cyclophosphamide-prednisolone) with the CP (cyclophosphamide-prednisolone) regimen. We selected CP instead of MP as the other arm of the randomized trial because 1) previous reports have confirmed that melphalan and cyclophosphamide are equally effective in the treatment of myeloma,[11, 12] 2) one of our members insisted on the superiority of the CP regimen to the standard MP regimen,[25] and 3) most members had experience with the MP regimen and were interested in investigating the CP regimen. Thus, we set out the present clinical trial considering that the comparison of effectiveness of VMCP with CP was equivalent to a comparison with MP. However, this assumption needs to be verified by comparing the effectiveness of the current CP regimen with an appropriate historical control, in which the standard MP regimen was employed.

The effectiveness of VMCP was evaluated not only by the comparison of survival curves but also by multiple statistical analyses. When the two groups were compared overall, the choice of chemotherapy (VMCP or CP) was not a significant prognostic factor associated with response or survival, and the difference between the survival curves of the two treatment groups was only marginally significant.

Patients with multiple myeloma are known to evolve into frank myeloma after passing through a protracted preclinical phase.[26] At present, it is difficult to differentiate patients still in a preclinical phase from those who should be diagnosed as smoldering or indolent myeloma in most institutions.[13, 27] However, even if patients receive chemotherapy while in the preclinical phase or while they have smoldering or indolent myeloma, their clinical course would probably be altered by it minimally, or at least the difference in the effectiveness of multi-drug combination chemotherapy and standard MP would be barely detectable.[28] In the present study, it is possible that some patients with preclinical or with smoldering or indolent myeloma were unintentionally classified as stage I or even stage II. These considerations led us to adopt a different approach, that is, we confined the evaluation only to those patients with stage III disease who already had a large tumor cell mass and would experience disease progression if observed without treatment.

Interestingly, the choice of chemotherapy (VMCP or CP) turned out to be a significant prognostic factor associated with response and survival in both univariate and multivariate analyses when the analysis was performed on the stage III subgroup. Moreover, the difference in the survival curves between the two treatment groups, which was only marginally significant for the whole group, turned out to be statistically significant by both the generalized Wilcoxon test and the logrank test. Thus, in the present study, the superiority of multi-drug combination chemotherapy was shown clearly in the treatment of stage III patients by an improved response rate and survival.

Harley et al.[2] reported an improved survival of stage III patients treated with combination chemotherapy. However, their study was criticized because the route of administration of melphalan differed between treatment groups.[29]

Although the design of our study may have been flawed by the fact that the comparison of effectiveness was with CP and not MP, this is the third prospective randomized trial that has demonstrated an improved response rate and survival for multi-drug combination chemotherapy. However, this result was obtained only among stage III patients. Considering the unique characteristics of multiple myeloma, further investigation into the pathophysiology of this disease is necessary, and hopefully, future advances will lead to improvements in therapy.

ACKNOWLEDGMENTS

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