Posttreatment M-Protein Nadir Level Is a Significant Prognostic Factor Associated with Survival in Multiple Myeloma

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In the present study 142 patients with myeloma (102 with IgG M-protein and 40 with IgA) treated with either VMCP (65 patients) or MMCP (77 patients) as remission induction therapy were retrospectively analyzed. Response to treatment was evaluated in terms of a more-than-50% fall of pretreatment M-protein and the posttreatment M-protein nadir. Though significantly more patients treated with MMCP achieved partial response (PR) as compared with those treated with VMCP (*P*=0.019) and though patients achieving PR showed a significantly longer survival than those with less responsiveness (*P*=0.0091), the difference in survival curves between the two treatment groups was not significant (*P*=0.1871). The difference in response between the treatment groups evaluated in terms of posttreatment nadir was not significant (*P*=0.507). Multivariate analysis identified posttreatment M-protein nadir as a significant prognostic factor associated with survival, along with 3 other factors: sex, performance status, and hemoglobin. The lack of difference between the survival curves for patients treated with the 2 regimens despite the significantly different response rates evaluated in terms of percent fall of pretreatment M-protein levels was considered to be due to the lack of a difference in the ability to induce a deep posttreatment nadir between the regimens. Posttreatment M-protein nadir is an important prognostic factor associated with survival and should be included in the evaluation of the efficacy of chemotherapy.

Key words: Multiple myeloma — Evaluation of response — Chemotherapy — Posttreatment M-protein nadir — Statistical analyses

A lack of correlation between an improved response rate and survival benefit in comparing different chemotherapeutic regimens has been a major concern of myeloma trialists.[1–3] Response in most studies has been defined according to the criteria of the Chronic Leukemia-Myeloma Task Force,[4] where partial response (PR) is defined as a more-than-50% reduction of the pretreatment level of M-protein. However, will a posttreatment M-protein level of 5,000 mg/dl in a patient whose pretreatment M-protein level was 10,000 mg/dl lead to the same survival as a posttreatment level of 1,500 mg/dl in another patient who shared the prognostic factors and whose pretreatment level was also 10,000 mg/dl? According to the above criteria, the response in each of these patients is equally defined as PR. Recently, complete remission (CR) has been defined and has been reported to be associated

with better survival,[5] which could imply that a profound decrease of M-protein *per se* is important.

In the present study, we focused on posttreatment M-protein nadir level and evaluated its relevance to survival.

PATIENTS AND METHODS

Patients From April 1984 to March 1993, 178 patients were diagnosed as having frank multiple myeloma at the hospitals of the Nagoya Myeloma Cooperative Study Group according to the diagnostic criteria set by the Southwest Oncology Group.[6] Among the 178 patients, 82 patients were treated with the VMCP regimen in the early period of our continuous chemotherapeutic trials for multiple myeloma, and the remaining 96 patients were treated with the newly developed MMCP regimen (Table I), as remission induction therapy. Among the 178 patients, 29 patients had Bence Jones type myeloma and were

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Table I. Doses and Schedules of the Chemotherapy Regimens

Regimen	Dose (mg/m^2)	Route	Schedule
VMCP (q3wks)			
Vincristine	1.0	i.v.	day 1
Melphalan	4.0	p.o.	day 1–4
Cyclophosphamide	66.7	p.o.	day 1–4
Prednisolone	20.0	p.o.	day 1–4
MMCP (q3wks)			
MCNU[a]	33.0	i.v.	day 1
Melphalan	4.0	p.o.	day 1–4
Cyclophosphamide	66.7	p.o.	day 1–4
Prednisolone	20.0	p.o.	day 1–4

a) MCNU, ranimustine.

excluded from the study because the number of the patients was too small and because Bence Jones protein exhibits different responses to treatment from serum M-protein. In addition, 7 patients who died before the start or the completion of the first course of chemotherapy were excluded because the data of posttreatment nadir M-protein level were not available. Accordingly, 142 patients composed of 102 (71.8%) IgG myeloma and 40 (28.2%) IgA myeloma patients were studied.

Pretreatment M-protein level To evaluate the distribution of the patients with IgG myeloma and those with IgA myeloma with regard to pretreatment M-protein levels, the patients were divided into 3 groups; less than 5,000 mg/dl for IgG pretreatment level and less than 2,500 mg/dl for IgA, between 5,000 and 7,000 for IgG and between 2,500 and 5,000 for IgA, and more than 7,000 for IgG and more than 5,000 for IgA.

Response evaluated in terms of percent fall of pretreatment M-protein level Response to treatment was evaluated based on the criteria proposed by the Chronic Leukemia-Myeloma Task Force,[4] where PR was defined as a more-than-50% reduction in pretreatment serum M-protein level and no change (NC) as a less-than-50% reduction.

Response evaluated in terms of posttreatment M-protein nadir level To evaluate posttreatment M-protein level of IgG myeloma and IgA myeloma patients, nadir levels of less than 2,000 mg/dl for IgG and less than 1,000 mg/dl for IgA M-protein were defined as the prominent group (PG), between 2,000 and 4,000 for IgG and between 1,000 and 2,000 for IgA as the intermediate group (IG), and more than 4,000 for IgG and more than 2,000 for IgA as the unsatisfactory group (UG).

Statistics Multiple statistical analyses were performed at Nagoya City Higashi General Hospital. Univariate analysis of the unadjusted association of each prognostic factor with the chemotherapeutic regimens was performed using Fisher's exact test. Pretreatment and posttreatment nadir

M-protein levels expressed as the mean and SD of results obtained from 65 patients for the VMCP group and from 77 patients for the MMCP group were compared using Student's *t* test. Survival was calculated from the start of therapy by the Kaplan-Meier method,[7] with differences assessed by the logrank test[8] and generalized Wilcoxon test.[9] Multivariate analysis using the stepwise Cox proportional hazards model[10] according to the PHGLM procedure of the SAS program[11] was performed to identify the important factors influencing survival. The following 12 characteristics were evaluated for prognostic value: age, sex, stage, pretreatment M-protein level (3 categories), posttreatment M-protein nadir level (3 categories), chemotherapy, response defined according to the criteria of the Chronic Leukemia-Myeloma Task Force, performance status, serum calcium, serum creatinine, hemoglobin, and albumin.

RESULTS

Table II shows the characteristics of the patients enrolled in the study. The differences in the distribution of 9 pretreatment prognostic factors (age, sex, stage, pretreatment M-protein level, performance status, serum calcium, serum creatinine, hemoglobin, and albumin) between VMCP and MMCP treatment groups were not statistically significant as evaluated by Fisher's exact test. It is noteworthy that there is no statistically significant difference in the distribution of patients according to pretreatment M-protein levels in 3 different categories between the treatment groups.

Table II also shows the distribution of the 142 patients according to the response evaluated in terms of 50%-or-more reduction in pretreatment M-protein level. Forty-four (57.1%) patients treated with MMCP and 24 (36.9%) treated with VMCP achieved PR, and the difference between the two regimens was significant ($P=0.019$). Fig. 1 shows survival curves for patients who achieved PR and for those who did not (NC), irrespective of the treatment administered; median survival for PR patients was 33.2 months, while that for NC patients was 19.6 months. The difference between the two curves was statistically significant. Table II also shows the distribution of the 142 patients evaluated in terms of posttreatment M-protein nadir level under the 2 regimens. The distributions of the patients into the 3 different categories (PG, IG, and UG) showed no statistically significant difference ($P=0.507$). Fig. 2 shows survival curves for patients categorized according to posttreatment M-protein nadir levels. The differences among the survival curves for the 3 categories, irrespective of the treatment given, where median survival for PG was 34.5 months, that for IG was 30.9 months, and that for UG was 14.7 months, were statistically significant. A comparison of the mean pretreatment M-pro-

tein levels and the mean posttreatment M-protein nadir levels of the 142 patients without categorization between the treatment groups showed no difference (Table III), consistent with the results in Table II, where analyses were performed on the categorized M-protein levels.

Fig. 3 shows survival curves for patients treated with MMCP or VMCP; the difference between the curves was not significant.

Twelve different pre- and posttreatment characteristics were evaluated for prognostic value (influence on sur-

vival) using the stepwise Cox proportional hazards model.[10] The result is shown in Table IV. Four factors, posttreatment M-protein nadir level, sex, performance status, and hemoglobin, were identified as significant.

DISCUSSION

In lymphoid neoplasms, reduction of tumor burden is considered to be associated with improved survival. In myeloma, serum M-protein level is an indicator of the

Table II. Characteristics of Patients

|	VMCP (n=65)	MMCP (n=77)	P value[a]
Age			
≥65 years	28	35	0.866
<65 years	37	42	
Sex			
Male	33	42	0.736
Female	32	35	
Ig class			
IgA	22	18	0.192
IgG	43	59	
Stage			
I	6	9	0.875
II	18	19	
III	41	49	
Pretreatment M-protein level (mg/dl)			
IgG<5,000 or IgA<2,500	29	22	0.095
IgG 5,000≤<7,000 or IgA 2,500≤<5,000	18	22	
IgG≥7,000 or IgA≥5,000	18	33	
Response evaluated by percent fall			
PR (≥50%)	24	44	0.019
NC (<50%)	41	33	
Posttreatment M-protein nadir level (mg/dl)			
PG (IgG<2,000 or IgA<1,000)	20	31	0.507
IG (IgG 2,000≤<4,000 or IgA 1,000≤<2,000)	26	25	
UG (IgG≥4,000 or IgA≥2,000)	19	21	
Performance status			
0–1	37	50	0.388
2–4	28	27	
Calcium (mg/dl)			
≥11.5	2	3	1.000
<11.5	63	74	
Creatinine (mg/dl)			
≥2.0	8	13	0.486
<2.0	57	64	
Hemoglobin (g/dl)			
≥8.5	42	52	0.726
<8.5	23	25	
Albumin (g/dl)			
≥3.5	38	41	0.612
<3.5	27	36	

a) By Fisher's exact test.
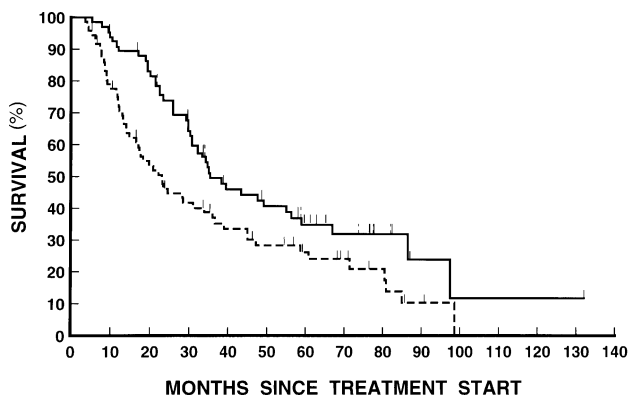
Fig. 1. Survival curves for patients achieving PR (solid line) and those assessed as NC (broken line). The tick marks indicate patients alive at the indicated time point. The difference between the curves was significant by both the generalized Wilcoxon test ($P=0.0014$) and the logrank test ($P=0.0091$). PR, partial response; NC, no change.
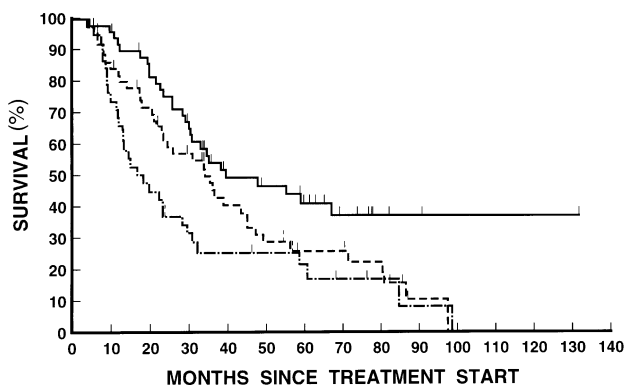

Fig. 2. Survival curves for patients according to the posttreatment M-protein nadir levels. The differences among the curves were significant by both the generalized Wilcoxon test ($P=0.0008$) and by the logrank test ($P=0.0032$). PG (——), prominent group (IgG<2,000 mg/dl or IgA<1,000 mg/dl); IG (----), intermediate group (IgG 2,000≤<4,000 mg/dl or IgA 1,000≤<2,000 mg/dl); UG (----), unsatisfactory group (IgG≥ 4,000 mg/dl or IgA≥2,000 mg/dl).

tumor burden, and its reduction after chemotherapy is assumed to be a sign of response. However, despite the fact that more patients attain PR when given several newly developed combination chemotherapies, the overall survival has not been significantly improved.[1–3] This is consistent with our findings, i.e., although survival curves for the patients achieving PR and for those with less responsiveness are significantly different (Fig. 1), and although significantly more patients treated with newly
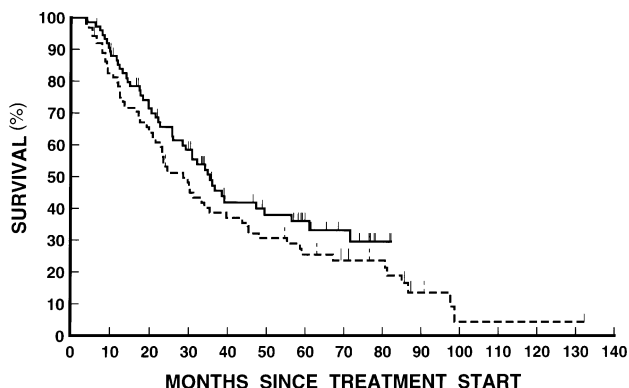

Fig. 3. Survival curves for patients treated with MMCP (solid line) or VMCP (broken line). The difference between the curves was not significant by either the generalized Wilcoxon test ($P=0.1440$) or the logrank test ($P=0.1871$).

Table IV. Cox Proportional Hazards Model Analysis of Survival

Prognostic factor	β	P value	Risk ratio
Sex	−0.605628	0.0055	0.546
M-Protein nadir level	0.451689	0.0006	1.571
Chemotherapy	−0.273683	0.1948	0.761
Performance status	0.566605	0.0068	1.762
Hemoglobin	−0.474634	0.0319	0.622

The P values of 7 other factors did not reach the 0.2 level and these factors were omitted.

Table III. Comparison of Mean Pretreatment M-Protein Levels and Posttreatment Nadir Levels in the Treatment Groups

Regimen	N	Pretreatment			Posttreatment nadir		
		Mean (mg/dl)	SD (mg/dl)	$P^{a)}$	Mean (mg/dl)	SD (mg/dl)	$P^{a)}$
VMCP	65	5,311	3,031	0.0772	3,201	2,452	0.4626
MMCP	77	6,182	2,894		2,919	2,194	

a) Difference assessed by Student's *t* test.

developed MMCP attained PR as compared with those treated with VMCP (Table II), the difference between the survival curves for the two treatment groups (Fig. 3) is not significant.

Based on the report by Gore et al.[5] claiming that complete disappearance of serum M-protein was associated with better survival, we evaluated posttreatment M-protein nadir levels in the 142 patients. As depicted in Fig. 2, survival curves for the patients grouped according to the posttreatment M-protein nadir levels (PG, IG, and UG) showed a statistically significant difference. However, the distribution of the patients grouped as PG, IG, and UG was not statistically significantly different (P=0.507) between the two treatment groups (Table II). The possibility of a biased distribution of the patients according to the pretreatment M-protein levels between the treatment groups was ruled out by Fisher's exact test (Table II). The possibility that the lack of difference in pretreatment M-protein levels and posttreatment M-protein nadir levels between the treatment groups was due to the categorization was ruled out by an analysis using the mean data of the 142 patients using Student's t test (Table III). Although it was not statistically significant, there seems to exist a difference in the pretreatment M-protein level between the VMCP and MMCP groups (5,311 vs 6,182), which could possibly have favorably influenced the results in the MMCP group when the efficacy of chemotherapy was evaluated in terms of percent fall of pretreatment M-protein level in Table II.

We interpret these results as indicating that posttreatment M-protein nadir level is more important than the percent fall of pretreatment M-protein level in the evaluation of efficacy of chemotherapy, because the lack of difference in the survival curves for the two treatment groups with significantly different response rates seemed to be ascribed to the lack of difference in posttreatment M-protein nadir levels between them. We then conducted a multivariate analysis to identify prognostic factors using a stepwise Cox proportional hazards model. As shown in Table IV, posttreatment M-protein nadir level, sex, performance status, and hemoglobin, among which posttreatment M-protein nadir is the only treatment-related variable, were identified as significant prognostic factors influencing survival. This result seems to support our interpretation.

Evaluation of response in terms of more-than-50% reduction of pretreatment M-protein level involves the risk of identifying the response of patients with high posttreatment nadir levels as PR if the pretreatment levels were very high, and thus might group together both true responders and patients with less responsiveness. This may explain why the apparently improved response rate was not associated with a survival benefit. We then considered whether adoption of a criterion of more-than-75% reduction of pretreatment M-protein level according to SWOG[12] would be more appropriate than the less strict criterion of the Chronic Leukemia-Myeloma Task Force. However, because there was no significant difference in the survival curves for patients with more-than-75% reduction and for those with less response in our preliminary study (data not shown), we discontinued this line of study.

Palmer et al. criticized current evaluation methods[13] and we now propose that evaluation of response in terms of posttreatment M-protein nadir would extract true responders more effectively than is possible on the basis of percent fall of pretreatment M-protein level. Our results suggest that a treatment providing a significantly lower posttreatment nadir than another treatment would also afford a significant improvement in survival over the other treatment. We should continue searching for a treatment to further lower M-protein, and we support the idea of intensified treatment aimed at CR.[5]

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