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A randomized study comparing VMCP and MMPP in the treatment of multiple myeloma

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Abstract *Purpose*: To compare VMCP, a multidrug combination chemotherapy comprising vincristine (VCR), melphalan (MPH), cyclophosphamide (CPM) and prednisolone (PSL), with MMPP comprising MPH, ranimustine (MCNU), procarbazine, and PSL as induction, to elucidate the value of alternating combination chemotherapy, and to search for an appropriate maintenance therapy in multiple myeloma. *Methods*: At 16 institutions in the Nagoya City area, we carried out a randomized trial of VMCP versus MMPP as the initial treatment. Patients who were refractory or resistant to the initial therapy were crossed over into the other arm (crossover trial). For patients who achieved a partial response (PR) or a minor response (MR) and in whom the paraprotein level ceased to decrease, the maintenance therapy was randomized either to an MPH/PSL combination (MP) or to alternating combination therapy (AT) with VMCP and MMPP. *Results*: In the 94 evaluable patients of the 111 enrolled, the response rate (PR rate) was 27.7% (13/47) in the VMCP arm and 44.7% (21/47) in the MMPP arm ($P = 0.0859$). The crossover trial resulted

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in a PR rate of 15.8% (3/19) for the VMCP → MMPP crossover and 14.3% (2/14) for the MMPP → VMCP crossover. The median survival time was 23.4 months for those initially begun in the VMCP arm and 24.9 months for those in the MMPP arm, showing a tendency for better survival during a follow-up of 2–6 years with MMPP treatment, but without statistical significance. The survival time of patients with progressive disease was significantly shorter than that of patients with PR, MR or no change (NC). However, there was no significant difference in the survival rate among those who achieved PR, MR, or NC. As to the maintenance therapy, there was no significant difference in survival between MP therapy and AT. Patients who reached a plateau phase survived significantly longer than those who did not. Except for six cases of grade 3 or 4 neurotoxicity in the VMCP arm, there was no significant difference in the hematologic or gastrointestinal toxicity between the two arms. *Conclusions*: We conclude that VMCP is less effective for myeloma than MMPP as the induction treatment, that alternating noncrossresistant chemotherapeutic combinations do not offer an advantage in multiple myeloma, and that patients who reach a plateau phase have a significantly longer survival time.

Key words Multiple myeloma · Noncrossresistant chemotherapy · Plateau phase

Introduction

Many combination chemotherapeutic trials have been conducted over the years to improve upon the single alkylating agent regimen for multiple myeloma [8]. Some studies have suggested that multidrug combination chemotherapeutic regimens produce better responses and survival rates than regimens using melphalan (MPH) or cyclophosphamide (CPM) with or without prednisone (PDN), although other studies have not been able to demonstrate an advantage [6, 8, 10, 12, 16, 17]. We have previously reported that VMCP, a multidrug combination chemotherapy comprising vincristine (VCR), MPH, CPM, and prednisolone (PSL), is superior to a combination of CPM and PSL in the treatment of stage III multiple myeloma [18]. In order to elucidate the value of alternating combination chemotherapy [6, 17] and the need for maintenance therapy [2, 8, 9], we initiated a randomized trial of a multidrug combination chemotherapy in December 1987 comparing VMCP and MMPP, the latter comprising MPH, ranimustine (MCNU), procarbazine (PCZ), and PSL. The aims of the trial were to: (1) compare VMCP and MMPP as the initial treatment for multiple myeloma; (2) determine the efficacy of a crossover in patients who were refractory to or resistant to the induction therapy; and (3) compare alternating VMCP and MMPP versus a combination of MPH and PSL as maintenance therapy. The analysis of the data also allowed us to determine the prognostic significance of the achievement of a plateau phase during therapy.

Material and methods

Patient population

A total of 111 patients with multiple myeloma were enrolled in this study at 16 institutions in the Nagoya City area between December 1987 and January 1991. Eligible patients were less than 80 years of age, previously untreated, with no significant concurrent cardiac, renal, or hepatic disease or other malignancies. Patients with indolent myeloma and smoldering myeloma were excluded from the study. All enrollments were made with the informed consent of the patients and/or guardians. Patients were randomized at the registration office, located at Anjo Kosei Hospital, for the type of induction therapy and maintenance therapy.

Treatment protocol

The VMCP regimen consisted of VCR (1 mg/m^2 i.v.) on day 1 and MPH (4.0 mg/m^2 orally), CPM (66.7 mg/m^2 orally) and PSL (30 mg/m^2 orally) on days 1 through 4. The MMPP regimen consisted of MPH (4.0 mg/m^2 orally) on days 1 through 4, MCNU (33.3 mg/m^2 i.v. infused over 1 h) on day 1, PCZ (66.7 mg/m^2 orally) and PSL (20 mg/m^2 orally) on days 1 through 7. Each cycle was repeated every 3 weeks, provided the leukocyte count had recovered to greater than 3000/μl and the platelet count to greater than 100 000/μl, and was continued until the serum and/or urine M-protein level ceased to decrease. The regimen was repeated for at least three cycles until disease progression was seen or until adverse effects prevented continuation.

Patients who were refractory to the initial regimen or whose paraprotein level either increased or remained stable within 15% in two successive measurements after an initial decrease were crossed over to the other arm.

Patients were given maintenance therapy if they had achieved a partial response (PR) or minor response (MR) and the paraprotein level ceased to decrease during the induction and/or crossover chemotherapy. The maintenance therapy was randomized to either the MPH/PSL (MP) combination or the alternating combination therapy (AT) with VMCP and MMPP. The MP regimen consisted of MPH (6.0–8.0 mg/m^2 orally) and PSL (40 mg/m^2 orally) on days 1 through 4 repeated every 6–8 weeks for 2 years or until progression of disease. The AT regimen consisted of alternating cycles of VMCP and MMPP using the same doses as used in the induction therapy repeated every 6–8 weeks for 2 years or until progression of disease.

Data analysis

Clinical efficacy was evaluated on the basis of criteria proposed by the Chronic Leukemia-Myeloma Task Force [3]. PR was defined as greater than a 50% reduction in the serum and/or urine M-protein level compared with the pretreatment value for at least 4 weeks without any signs of clinical deterioration. The non-PRs were classified into MR, no change (NC), or progressive disease (PD). MR was defined as a greater than 25% but less than 50% decrease in the paraprotein level for 4 weeks or longer or a greater than 50% reduction in the paraprotein level for less than 4 weeks without any

clinical deterioration. PD was defined as a greater than 25% increase in the paraprotein level compared with the pretreatment value or progression of disease as detected on the basis of clinical findings or laboratory tests. NC was defined as the status that was neither MR nor PD.

Patients were considered to have entered a plateau phase if they achieved a stable serum and/or urine M-protein level, exhibited a stable clinical picture, including the absence of progression of bone lesions, and were transfusion independent for a period of 6 months or longer.

Statistical analysis

Survival curves were obtained by the Kaplan-Meier method. The Chi-squared test was used to analyze patient characteristics, response rates, and frequency of adverse reactions. The generalized Wilcoxon test (GW) and log-rank test (LR) were used in the statistical analysis of survival. The closing date for statistical evaluation was 31 March 1995.

Results

Evaluable subjects

Of the 111 patients enrolled, 94 were evaluable. The reasons for the 17 exclusions were five because of prior therapy (two in the VMCP arm, three in the MMPP arm), three because of indolent myeloma (two VMCP, one MMPP), two because of hemodialysis (one VMCP, one MMPP), two because of nonsecretory myeloma (two VMCP), and five for other reasons (two VMCP, three MMPP). There was no significant difference in the exclusions between the two arms.

The profile of the evaluable patients entered into the trial is given in Table 1. The median age for both the VMCP arm and the MMPP arm was 62 years. There were no statistically significant differences in the two arms when analyzed for age, type of M-protein, stage, peripheral white blood cell count, hemoglobin, performance status, serum calcium level, and other characteristics such as sex, bone lesions, bone marrow findings, and blood chemistry data (data not shown).

For the 94 evaluable subjects, the median and mean of the number of cycles administered in the two arms were 5 and 6.6 (range 1–27) in the VMCP arm and 5.5 and 6.3 (range 1–22) in the MMPP arm.

Response and survival

The initial induction therapy resulted in 13 PR (27.7%) and 15 MR (31.9%) among the 47 evaluable subjects in the VMCP arm and 21 PR (44.7%) and 14 MR (29.8%) among the 47 evaluable subjects in the MMPP arm, suggesting superiority of MMPP over VMCP, although the difference between the two PR rates was not statistically significant by a narrow margin ($P = 0.0859$).

Table 1 Patient characteristics (*VMCP* vincristine, melphalan, cyclophosphamide, prednisolone; *MMPP* ranimustine, melphalan, procarbazine, prednisolone)

	VMCP	MMPP
Number of cases entered	56	55
Number of evaluable cases	47	47
Age (years)		
32–59	17	17
60–69	22	16
70–79	8	14
Median	62	62
Type of M-protein		
IgG	25	33
IgA	11	7
IgD	3	0
Bence Jones	8	7
Stage (Durie and Salmon)		
I	3	1
II	16	10
III	28	36
(B symptom)	(7)	(8)
Peripheral blood		
WBC (/mm^3)		
$\geq$ 4000	29	31
3000–3999	11	14
2000–2999	7	1
1000–1999	0	1
Hb (g/dl)		
10.0–13.1	21	15
8.6–9.9	10	14
6.0–8.5	14	15
4.9–5.9	2	3
Performance status		
0	7	9
1	19	16
2	7	9
3	10	10
4	4	3
Ca (mg/dl)		
12.0–15.3	3	3
$\geq$12.0	44	44

The results of the crossover are shown in Table 2. Reasons for crossover were a paraprotein increase after a transient decrease in ten subjects in the VMCP arm and nine subjects in the MMPP arm and no change in the paraprotein level (within 15%) in two successive measurements in nine subjects in the VMCP arm and five in the MMPP arm. Four patients from each arm were excluded from analysis because they had been entered into the crossover despite achieving a greater than 15% reduction in the paraprotein level. Among the 14 evaluable subjects from the MMPP arm, 2 achieved a PR, while among the 19 evaluable subjects from the VMCP arm, 3 achieved a PR. Thus, the PR rates in patients who were refractory to or became resistant to the initial induction therapy were 14.3% in the VMCP arm and 15.8% in the MMPP arm.

The overall rates of response, including those who were excluded in the analysis of the crossover, were 15 PRs (31.9%), 18 MRs (38.3%), 11 NCs (23.4%), and

Table 2 Results of crossover trial (*PR* partial response, *MR* minor response, *NC* no change, *PD* progressive disease, *VMCP* vincristine, melphalan, cyclophosphamide, prednisolone, *MMPP* ranimustine, melphalan, procarbazine, prednisolone)

Initial effect	No. of patients	Outcome			
		PR	MR	NC	PD
MMPP → VMCP					
PR	4	2	1	1	
MR	4		1	2	1
NC	3		2	1	
PD	3		1	2	
Total	14	2	5	6	1
VMCP → MMPP					
PR	5	1		1	3
MR	4		2	1	1
NC	9	2	2	3	2
PD	1		1		
Total	19	3	5	5	6

3 PDs (6.4%) in the VMCP arm, and 27 PRs (57.4%), 13 MRs (27.7%), 3 NCs (6.4%), and 4 PDs (8.5%) in the MMPP arm.

For the maintenance therapy, 13 patients (8 VMCP, and 5 MMPP) were allocated to the MP arm, and 12 (5 VMCP and 7 MMPP) to the AT arm. There was no significant difference in survival between the two arms (data not shown.)

The survival curves of the evaluable cases in the VMCP arm and the MMPP arm are shown in Fig. 1. The median survival time was 23.4 months in the VMCP arm and 24.9 months in the MMPP arm. Although there was a trend toward better survival during 2–6 years of follow-up in the MMPP arm, there was no significant difference between the two arms ($P = 0.324$ by GW, and $P = 0.254$ by LR).

Figure 2 shows the survival curves stratified according to the final chemotherapeutic effect. There was no significant difference among the PRs, MRs, and NCs. The survival in the PD group was significantly shorter than in the PR group ($P = 0.0008$ by GW, $P < 0.0001$ by LR), the MR group ($P = 0.0198$ by GW, $P = 0.0027$ by LR) and the NC group ($P = 0.0368$ by GW, $P = 0.0304$ by LR).

A plateau phase was observed in 9 patients in the VMCP arm and in 20 patients in the MMPP arm. The incidence of the plateau phase was significantly higher in the MMPP arm than in the VMCP arm (42.6% vs 19.1%, $P = 0.0140$). The duration of the plateau was 6–12 months in eight patients (three VMCP, five MMPP), 13–18 months in eight patients (two VMCP, six MMPP), 19–24 months in seven patients (three VMCP, four MMPP), 25–30 months in four patients (one VMCP, three MMPP), and 37–45 months in two patients (both MMPP). Chemotherapy administered during the plateau phase was: VMCP in nine patients (two given VMCP induction, seven given MMPP induction), alternating VMCP/MMPP in seven patients (four VMCP, three MMPP), MP in six patients (three VMCP, three MMPP), and MMPP in six patients (all MMPP), and none in one patient (MMPP).

Figure 3 compares the survival times for patients who achieved a plateau versus those who did not. There was no significant difference between VMCP and MMPP regarding whether or not a plateau was achieved. Patients who achieved a plateau, however, survived significantly longer than those who did not achieve a plateau ($P = 0.0020$ by GW, $P = 0.0200$ by LR).

Adverse effects

Bone marrow suppression was the most common adverse effect during the induction therapy in both arms. The incidence of leukopenia and thrombocytopenia

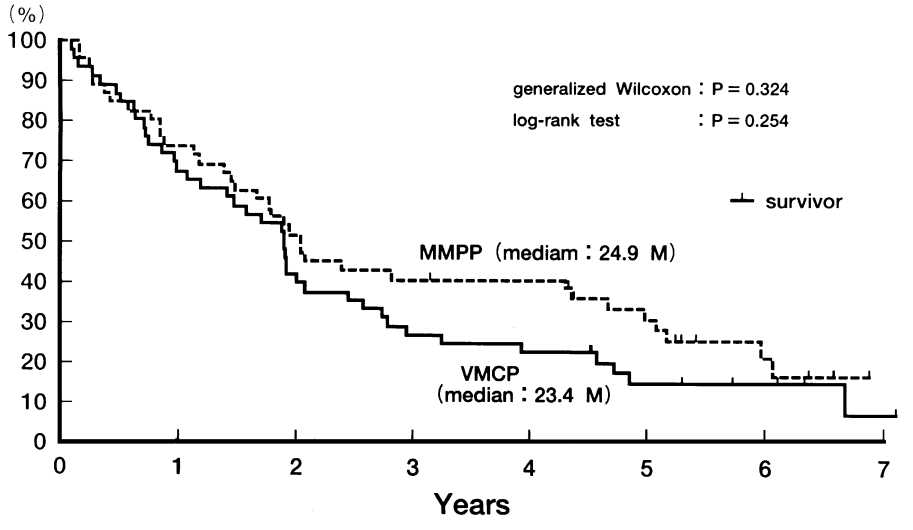

Fig. 1 Survival time of all evaluable patients (*VMCP* vincristine, melphalan, cyclophosphamide, prednisolone; *MMPP* ranimustine, melphalan, procarbazine, prednisolone)

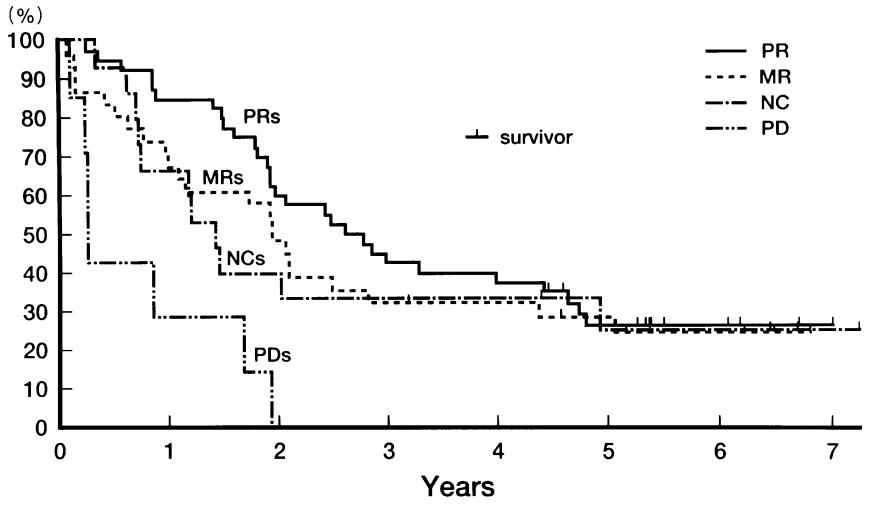

Fig. 2 Survival time according to the final chemotherapeutic effect (*PR* partial response, *MR* minor response, *NC* no change, *PD* progressive disease; *VMCP* vincristine, melphalan, cyclophosphamide, prednisolone; *MMPP* ranimustine, melphalan, procarbazine, prednisolone)

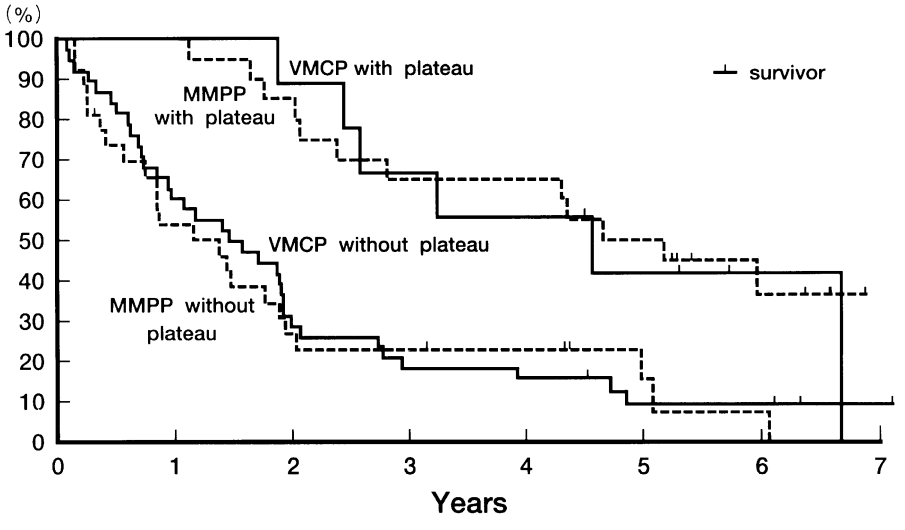

Fig. 3 Survival time of patients who achieved a plateau phase versus those who did not (*VMCP* vincristine, melphalan, cyclophosphamide, prednisolone; *MMPP* ranimustine, melphalan, procarbazine, prednisolone)

after the first and second cycles is shown in Table 3. The incidence of leukopenia with a white blood cell count of 2000/μl or less was 26% after the first cycle and 20% after the second cycle in the VMCP arm and 23% and 22%, respectively, in the MMPP arm. There was no significant difference in the incidence of leukopenia between the two arms.

Six patients with grade 3 or 4 neurotoxicity were observed in the VMCP arm. VCR was discontinued in one patient, changed to another vinca alkaloid with less neurotoxicity in one patient, and reduced in dosage in four patients.

There were no significant differences between the two arms with respect to other adverse effects, including anorexia, nausea, vomiting, and hepatotoxicity.

Discussion

Several multidrug chemotherapeutic regimens, such as VMCP, VCAP (VCR + CPM + doxorubicin (ADM) + PDN), VBAP (VCR + (1-3-bis(2-chloroethyl)1-nitrosourea (BCNU) + ADM + PDN), and ABCM (ADM + BCNU + CPM + MPH), have been reported for multiple myeloma [2, 8, 10, 12, 16–18], but it remains unclear which combination of drugs represents the best standard combination chemotherapy. This study shows that induction chemotherapy with MMPP achieved a higher PR rate than VMCP, although the difference did not reach statistical significance by a narrow margin ($P = 0.0859$). Since the degree of bone marrow suppression by the two regimens was similar, the dose intensities of VMCP and MMPP are likely to be similar. Because MPH and PSL were present in both arms, the difference in the PR rate was thought to represent the difference in the efficacy between MCNU + PCZ and VCR + CPM. The antimyeloma effects of MCNU, PCZ and CPM as single agents have previously been reported [8, 14, 19]. We have found no reports of VCR as a single agent, although it has been incorporated into several different multidrug regimens [1, 10, 17, 18]. It has been reported that a combination of VCR and PDN during the maintenance phase improves the survival of good-risk

Table 3 Comparison of leukopenia as a consequences of chemotherapy (*VMCP* vincristine, melphalan, cyclophosphamide, prednisolone, *MMPP* ranimustine, melphalan, procarbazine, prednisolone)

Regimen	WBC (/μl)	1st course		2nd course	
		Before	Nadir	Before	Nadir[a]
VMCP	≥4000	29	13	23	15
	3000–3999	11	9	13	6
	2000–2999	7	13	8	11
	1000–1999	0	10	1	8
	<1000	0	2	0	1
MMPP	≥4000	31	14	19	3
	3000–3999	14	6	15	14
	2000–2999	1	16	9	12
	1000–1999	1	10	2	8
	<1000	0	1	0	2

[a] Data from four patients in VMCP arm and six in MMPP arm were excluded because of difficulty in evaluation

patients [7], but it has also been reported that the addition of VCR to the firstline therapy does not improve survival [13]. We attribute the inferiority of VMCP to MMPP as an induction therapy to the inferior antimyeloma effect of VCR. In addition, VCR caused moderate to severe toxicity in six patients. Thus, we conclude that VCR should not be included in the firstline induction therapy for multiple myeloma.

The response rate to the crossover therapy in patients who became resistant to or were refractory to the induction chemotherapy was low. The MMPP → VMCP crossover resulted in two PRs (14.3%) and five MRs, while the VMCP → MMPP crossover resulted in three PRs (15.8%) and five MRs. The reason for the low rate may be partly because two of the drugs were used in both regimens, resulting in a lower antitumor activity of MCNU + PCZ in patients previously treated with VMCP or lower activity of VCR + CMP in patients previously treated with MMPP. In terms of the possible clinical significance of crossresistance, however, several clinical trials using combination chemotherapeutic regimens comprising alternating noncross-resistant drugs have not demonstrated superior clinical efficacy [4, 5, 15]. The Southeastern Cancer Study Group (SECSG) reported that when two chemotherapeutic regimens BCNU, CPM and PDN versus MPH and PDN were compared, only 10% of the patients who failed to respond to the initial regimen responded to the alternate regimen [4]. Another SECSG study showed that MP or a combination of PDN, ADM, azathioprine, and VCR as consolidation/maintenance therapy offers little advantage for patients who have responded to induction therapy with a combination of BCNU, CPM, and PDN [5]. In a single arm study, Morstyn et al. [15] failed to prolong survival using alternating, potentially noncrossresistant chemotherapeutic combinations. These studies indicate that multiple myeloma is not effectively controlled using presently available noncrossresistant chemotherapeutic regimens.

Concerning the comparison of survival rates between the two arms, the MMPP arm showed a trend towards better survival during a follow-up of 2–6 years, which reflected the higher rate of PR and larger proportion of patients achieving a plateau phase. However, no significant difference was seen in the overall survival between the two arms. This suggests that MMPP offers no long-term benefit over VMCP.

The present study also demonstrated that patients with PD had a significantly poorer survival than those with PR, MR, or NC. There were no significant differences in survival among those with PR, MR, and NC. Thus, we conclude that PD despite chemotherapy is associated with a poorer prognosis.

The plateau phase in multiple myeloma is a state in which PD does not occur despite persistence of significant bone marrow infiltration by malignant plasma cells and elevation in the paraprotein level [8, 9]. In our study, the plateau phase lasted for 6–26 months in the VMCP arm and 6–45 months in the MMPP arm, with a significant prolongation of survival. However, entry into a plateau phase did not significantly increase the percentage of long-term survivors. Administration of various chemotherapy regimens during the plateau phase did not influence the M-protein level or the clinical condition, in agreement with previous studies [8, 9]. A difficulty with the plateau phase in clinical situations, however, is that the plateau is identified only retrospectively after observation over a 6-month period and it is difficult to identify at the outset which patients will enter a plateau phase [11]. Furthermore, all patients who enter a plateau phase eventually experience PD. Prolongation of the plateau phase would be a significant breakthrough in prolonging the survival of patients with multiple myeloma.

In summary, our study indicated that VMCP is less effective for myeloma than MMPP as the induction treatment, that alternating noncrossresistant chemotherapy would not produce significant effects, that patients who experienced PD despite chemotherpy have a poor prognosis, and that achievement of a plateau phase prolonged survival significantly. Myeloma remains an incurable disease. However, the development of agents which promote entry into or prolong the duration of the plateau phase may be of clinical value in the treatment of multiple myeloma.

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