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Prognostic factors in multiple myeloma treated with prednisolone and sequential melphalan and ifosfamide: MIP combination chemotherapy*

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Abstract

Response rates and survival times were studied in 47 patients who had multiple myeloma and who were being treated with Prednisolone and sequential Melphalan and Ifosfamide (MIP therapy). The clinical response was determined by objective parameters such as the reduction of M-protein level, tumor volume and healing of bone destruction. Twenty-eight of the patients (59.6%) responded to the MIP therapy. The 50% survival time as followed from the initiation of treatment to death was 19 months. Of the prognostic factors, the age (greater than or equal to 70 years), clinical stage III of Durie and Salmon, hypercalcemia, extensive bone lesions, and the patho-morphological type IV of Brucher were associated with a decreased life-span. Therefore, MIP therapy was more effective in poor risk (high tumor mass group) than in good risk (low or intermediate tumor mass group) patients, but the survival of patients on MIP therapy was shorter in the poor risk group than in the good risk one. In addition, the group which responded rapidly (i.e. within 2-5 weeks) had longer remission and longer survival than the group which improved slowly (i.e. after 6-16 weeks).

KEYWORDS: multiple myeloma, prognostic factor, combination chemotherapy

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PROGNOSTIC FACTORS IN MULTIPLE MYELOMA TREATED WITH PREDNISOLONE AND SEQUENTIAL MELPHALAN AND IFOSFAMIDE: MIP COMBINATION CHEMOTHERAPY

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Abstract. Response rates and survival times were studied in 47 patients who had multiple myeloma and who were being treated with Prednisolone and sequential Melphalan and Ifosfamide (MIP therapy). The clinical response was determined by objective parameters such as the reduction of M-protein level, tumor volume and healing of bone destruction. Twenty-eight of the patients (59.6%) responded to the MIP therapy. The 50% survival time as followed from the initiation of treatment to death was 19 months. Of the prognostic factors, the age (≧ 70 years), clinical stage III of Durie and Salmon, hypercalcemia, extensive bone lesions, and the patho-morphological type IV of Brücher were associated with a decreased life-span. Therefore, MIP therapy was more effective in poor risk (high tumor mass group) than in good risk (low or intermediate tumor mass group) patients, but the survival of patients on MIP therapy was shorter in the poor risk group than in the good risk one. In addition, the group which responded rapidly (*i.e.* within 2-5 weeks) had longer remission and longer survival than the group which improved slowly (*i.e.* after 6-16 weeks).

Key words : multiple myeloma, prognostic factor, combination chemotherapy.

In recent years, the incidence of multiple myeloma has been increasing in proportion to the prolongation of life-span. Combination chemotherapy for multiple myeloma has improved response rates and survival times (1, 2, 3, 4); for example, in comparison with either Melphalan alone, or with Melphalan and Prednisolone, drug combinations which include Vincristine (an antimitotic drug) and Adriamycin (an anthracycline antibiotic) have resulted in high response rates and longer survival times. Multiple myeloma which is a malignancy of plasma cells that has many manifestations. Correlations of pretreatment values with response rates and survival times have been evaluated by, for example, Alexanian *et al.* who evaluated prognostic factors such as age, sex, race, hemoglobin concentration, serum calcium, and myeloma protein levels in patients receiving Melphalan and Prednisone. However, previous reports concerning prognostic factors mainly consisted of analyses of patients treated with Melphalan alone or with intermittent Melphalan and Prednisone. In this report,

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the prognostic factors of patients treated with multi-combination therapy, Melphalan and Ifosfamide (Z-4942), were evaluated, as well as the relationship between the clinical profiles of multiple myeloma and the effects of combination chemotherapy.

PATIENTS AND METHODS

This report consists of an analysis of 47 patients with multiple myeloma registered during the period October 1975 to December 1980. Twenty patients (40.6 %) were male, and the median age at the initiation of treatment was 65 years, ranging from 47 to 79 years. The 60-69 year age was the largest group. The protocol for MIP therapy is illustrated in Fig. 1. The diagnosis required two or more of three categories as listed in Table 1.

Clinical response was evaluated on the basis of a reduction of the M-protein level to less than 50 % of the pretreatment value. Survival curves were determined from the beginning of treatment according to the Kaplan-Meier method (5). Statistical differences in survival curves between individual groups were evaluated using the generalized Wilcoxon test (6). In December 1980, thirty of 47 patients (63.8 %) died. The survivors were followed for at least 13 months. The relationship of prognostic factors such as age, sex, M-protein type, tumor-formation (7), clinical stage (8), hemoglobin concentration, corrected calcium (9), albumin level, M-protein level, the extent of bone lesions, patho-morphological type (10), and time to remission, to the response rate and survival was evaluated.

TABLE 1. CRITERIA FOR DIAGNOSIS

Ⅰ. Morphological findings	
1) Plasmacytoma on tissue biopsy	
2) Nodular infiltration of plasma cells on bone biopsy specimen	
3) Myelogram: plasmacytosis ≧ 30 % plasma cells	
presence of atypical plasma cells	
Ⅱ. Bone lesion	
1) Punched-out, compression fracture, lytic bone, and advanced osteoporosis on bone X-ray film	
2) Presence of abnormal uptake on bone scintigram	
Ⅲ. Monoclonal globulin spike	
1) Serum M-protein level	
IgG peak ≧ 2 g/dl	
IgA peak ≧ 1 g/dl	
2) Urine B-J protein excretion ≧ 2 g/day	
3) Decreasing of normal immunoglobulin	
IgM ≦ 50 mg/dl	
IgA ≦ 100 mg/dl	
IgG ≦ 600 mg/dl	

Diagnosis confirmed when two or more out of Ⅰ, Ⅱ, and Ⅲ are documented.

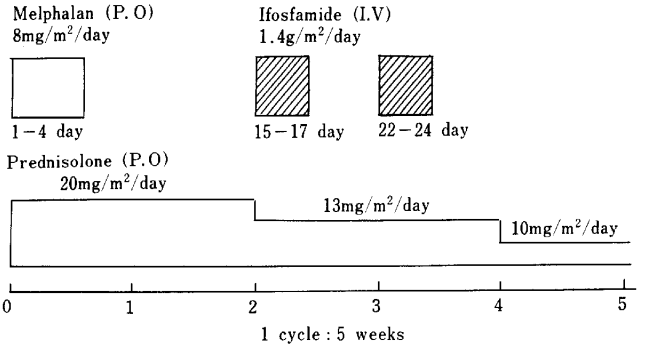

Fig. 1. Protocol of Prednisolone and sequential Melphalan and Ifosfamide (MIP). Melphalan (p.o.): 8 mg/m²/day day 1-4; Ifosfamide (i.v.): 1.4 g/m²/day day 15-17 and day 22-24; Prednisolone (p.o.): 20 mg/m²/day day 1-14, 13 mg/m²/day day 15-28, 10 mg/m²/day day 29-35
These regimens are continued every 5 weeks for at least 2 courses.

RESULTS

The clinical response of multiple myeloma treated with MIP was as follows; six of 7 patients (85.7 %) had an objective response as shown by more than 50 % regression in the product of the two diameters of the plasma cell tumor. Four of 35 patients (11.4 %) demonstrated radiographic evidence of recalcification or disappearance of lytic bone lesions. Over 50 % reduction in M-protein level was achieved in 59.6 % and the 50 % survival time was 19 months from the beginning of treatment. The correlation of the response rate and survival time with a variety of clinical parameters was evaluated in detail.

Age, sex, M-protein type, and tumor formation. Table 2 demonstrates the influence of age, sex, M-protein type, and tumor formation on the response rate and survival time. The response rate of 12 patients older than 70 years was higher than that of patients less than 70 years, but the survival was significantly shorter ($p = 0.02$). Female patients with IgA-peak, lambda-chain, and plasma cell tumors had a higher response rate associated with longer survival than male patients with IgG-peak, kappa-chain, and non-plasma cell tumors. However, there was no statistical significant difference between the two groups in any factors besides age with respect to survival.

Clinical stage, hemoglobin concentration, corrected calcium, albumin level, M-protein level, and the extent of bone lesion. The present series classified patients according to the criteria of Durie and Salmon (11). Of the patients, eleven were classified as stage I + II and thirty-six as stage III. Table 3 shows that MIP therapy was more effective in stage III than in stage I + II, but that the survival time in stage III (17.5 months) was shorter than in stage I + II (30.0 months). There was a significant difference between these groups as shown in Fig. 2 ($p = 0.05$).

The infiuence of individual clinical features, such as hemoglobin concentra-

TABLE 2. INFLUENCE OF AGE, SEX, M-PROTEIN TYPE, AND TUMOR-FORMATION ON RESPONSE RATE AND SURVIVAL

Patient group	Total no.	Response rate (%)	50% Survival (Month)	
I. Age				
< 70 years	35	54.3	21.5	p=0.02
≧ 70 years	12	75.0	10.5	
II. Sex				
Male	20	45.0	15.5	NS
Female	27	70.4	26.5	
III. M-protein type				
IgG	31	45.2	20.5	NS
IgA	13	84.6	21.5	
IgD	1	100.0	15.5	
BJ-only	2	100.0	11.5, 18.5	
Kappa	29	55.2	15.0	NS
lambda	18	66.7	21.5	
IV. Tumor-formation				
(+)	7	85.7	20.5	NS
(−)	40	55.0	18.5	

NS=not significant

TABLE 3. INFLUENCE OF CLINICAL STAGE AND PATHO-MORPHOLOGICAL TYPE ON RESPONSE RATE AND SURVIVAL

Patient group	Total no.	Response rate (%)	50% Survival (Month)	
I. Clinical stage				
I + II	11	45.5	30.0	p=0.05
III	36	63.9	17.5	
II. Patho-morphological type				
I + III	14	57.1	20.5	
II	8	50.0	39.5	p=0.04
IV	25	64.0	15.5	

NS=not significant

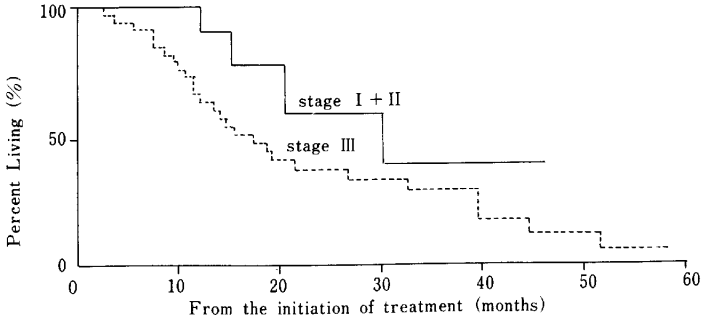

Fig. 2. Survival curve for patients grouped by the clinical stage of Durie and Salmon. The 50% survival; stage I + II 30.0 months and stage III 17.5 months. (p = 0.05)

tion, corrected calcium, albumin level, M-protein level, and the extent of bone lesions, on the response rate and survival time is summarized in Table 4. In this series, the response rates were paradoxically higher in all clinical features of the poor risk group (high tumor mass group) compared to the good risk group (low and intermediate tumor mass group), especially with respect to albumin level. On the other hand, patients in the poor risk group had a shorter survival time than those in the good risk one, in particular there were significant differences between the two groups devived by corrected calcium ($p = 0.04$) and the extent of bone lesions ($p = 0.01$). No statistical difference between the groups with a hemoglobin value $\geqq 8.5$ g/dl and with a hemoglobin value < 8.5 g/dl was found.

Patho-morphological type. In our report, type I of Brücher was defined by evidence of solitary plasmacytoma, and type II by evidence of osteoporosis with either bone marrow plasmacytosis $\geqq 50$ % or severe anemia (Hb. < 8.5 g/dl). Type III was diagnosed by evidence of multiple lytic bone lesions with neither bone marrow plasmacytosis $\geqq 50$ % nor severe anemia (Hb. < 8.5 g/dl) in accordance with the stage III (or stage II) of Durie and Salmon. Type IV was diagnosed by evidence of advanced lytic bone lesions with either bone marrow plasmacytosis or severe anemia described as in type II (10, Fig. 3). Analyses of the survival for patients divided by patho-morphological type are presented here for the first time. Table 3 shows the response rates and survival times in individual types. The response rates seem to be similar and the correlation of types with survival was assessed. Type II showed the longest survival of the three and there was a sig-

TABLE 4. INFLUENCE OF DIFFERENT RISK FACTORS ON RESPONSE RATE AND SURVIVAL

Patient group	Total no.	Response rate (%)	50 % Survival (Month)	
I. Hb.-concentration				
$\geqq 8.5$ mg/dl	22	50.0	20.5	NS
< 8.5mg/dl	25	68.0	19.5	
II. Corrected Ca. concentration				
$\leqq 11$ mg/dl	38	57.6	21.5	p=0.04
> 11 mg/dl	9	66.7	11.5	
III. M-protein level				
IgG $\leqq 5$ g/dl	25	44.0	30.0	NS
IgG > 5 g/dl	6	50.0	13.5	
IV. Alb.-concentration				
$\geqq 3$ g/dl	36	50.0	20.5	NS
< 3 g/dl	11	90.9	15.5	
V. Bone lesion				
scale 0, 1, 2	22	59.1	39.5	p=0.01
scale 3	25	60.0	12.0	

NS= not significant

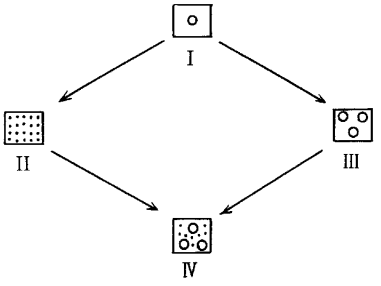

Fig. 3. A schema of the patho-morphological types of Brücher
Type 1 : Solitary lesion
Type 2 : Diffuse proliferation (osteoporosis)
Type 3 : Multiple lesions
Type 4 : Diffuse proliferation with multiple lesions

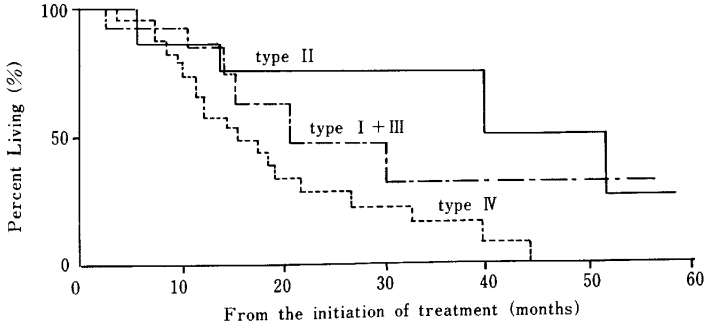

Fig. 4. Survival curve for patients grouped by the patho-morphological types of Brücher. The 50 % survival; type I + III 20.5 months, type II 39.5 months, and type IV 15.5 months. (p=0.04)

nificant difference between type II (39.5 months) and type IV (15.5 months) as shown in Fig. 4 (p=0.04). This observation was especially noteworthy.

Time to remission. In this analysis, twenty-eight of 47 patients responded to MIP therapy and sixteen (61.5 %) of them required 2-5 weeks to achieve over 50 % reduction of M-protein level. Twelve (38.5 %) required 6-16 weeks. Disappearance of M-peak was demonstrated in 6 cases of the rapidly responding group and in 2 cases of the slowly responding one. Also, patients who responded rapidly had a longer remission and a longer survival than those who responded slowly. There was a significant difference between these two groups with respect to survival as shown in Table 5 (p=0.05).

TABLE 5. CORRELATION OF TIME TO REMISSION WITH REMISSION DURATION AND SURVIVAL

Time to remission (weeks)	Total no.	Med. remission duration n (Month)	50 % Survival (Month)	
2 – 5	16	13.25 + α	20.5	p=0.05
6 – 16	12	6.25 + α	17.5	

DISCUSSION

There is growing evidence that combination chemotherapy incorporating alkylating agents is effective in prolonging the survival of patients with multiple myeloma (12). In this report, 47 patients with multiple myeloma diagnosed by unequivocal criteria received at least two courses of MIP therapy. Twenty-eight of these patients responded to MIP therapy and achieved more than a 50 % reduction in M-protein level. This result was similar to that reported by other investigators (13). Recalcification or disappearance of lytic bone lesions was demonstrated in four of 35 cases, which corresponds to the response rate reported by others (14). Patients with multiple myeloma persent many variations in the frequency and severity of clinical manifestations. The prognosis is made by evaluating clinical parameters at presentation and the appropriate chemotherapy regimen in an individual case is selected. The present report evaluated the prognostic importance of certain clinical features.

Firstly, the response rate of patients classified by age, sex, M-protein type, and tumor-formation was high especially in patients older than 70 years, who were female and had the IgA-peak, lambda-chain, and tumor-forming type. These conclusions differed from those reported by Alexanian who demonstrated that no marked difference in the response rate occured between two groups classified by age, sex, and M-protein type (15). In regard to survival, the present report identified a significant difference between the two groups classified by age. Ten of 12 patients older than 70 years had a high tumor mass load, that is, corresponding to the stage III of Durie and Salmon. Alexanian showed that there were significant differences in survival between patients older than 65 years and patients less than 55 years old (15).

The clinical staging system of Durie and Salmon, which was related to the rate of M-protein synthesis and to the total tumor mass, was determined from the hemoglobin concentration, serum calcium level, M-protein production rate, and the extent of bone lesions (8). Significant differences in survival were found between individual stages. Woodruff also demonstrated significant differences in survival for patients at each of the three different stages (16). On the other hand, Alexanian defined the present tumor mass from criteria for hemoglobin concentration, corrected calcium, and M-protein production rate and excluded criteria for the extent of bone lesions because of equivocal data (15). Thus, he made clear that patients with severe anemia, hypercalcemia, or a high rate of M-protein production had a significantly shorter survival than those without these features. The present report also confirms that groups in stage I + II have a significantly longer survival than stage III. Furthermore this significant difference emerged not from such clinical parameters as hemoglobin concentration, albumin level, and M-protein level, but from corrected calcium and the extent of bone lesions. The extent of bone lesions, including the corrected calcium, seem to be the most important prognostic factor. Thus, to evaluate the extent of bone le-

sions might be of benefit in predicting the prognosis.

As described previously, the severity of anemia might not be related to the prognosis for multiple myeloma. Though patients with severe anemia (Hb$<$ 8.5 g/dl) have been classified as stage Ⅲ according to the criteria proposed by Durie and Salmon and are thought to have a poor prognosis, in reality, patients with severe anemia who have radiographic evidence of osteoporosis, not accompanied by lytic bone lesions, may have a good prognosis. In the present paper, type Ⅱ of Brücher, corresponding to stage Ⅲ (or stage Ⅱ) of Durie and Salmon, which has a charactor of osteoporosis with either severe anemia or bone marrow plasmacytosis, demonstrated a longer survival than type Ⅳ or type Ⅰ + Ⅲ. Therefore, it is important to recognize the possibility that the frequency of type Ⅱ in stage Ⅲ influences the survival time of stage Ⅲ.

Hematopoietic malignancies other than multiple myeloma achieve complete remission quickly, then have a long remission and therefore a long survival. These findings also apply to multiple myeloma. In other words, patients who responded rapidly to MIP therapy and achieved over 50 % reduction in M-protein level would have longer remissions and therefore longer survival times. Furthermore patients achieving remission sooner (*i.e.* within 2-5 weeks) had a higher degree of reduction rate than those achieving remission later (*i.e.* after 6-16 weeks). These observations differ from those reported by Hobbs (17) and Alexanian (15), who considered that rapidly responding patients relapsed early and resulted in a short remission and survival. This difference is due to the fact that patients in this report received MIP therapy, devised to respond to chemotherapy even in patients resistant to Melphalan or Ifosfamide alone, whereas patients in the reports by Hobbs or Alexanian received Melphalan alone or Melphalan and Prednisone. Thus, intensive chemotherapy in the future should be done to achieve marked reduction of the M-protein production rate as quickly as possible (18).

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