The Korean Journal of Internal Medicine
Vol. 2, No. 1, January, 1987

Multiple Myeloma in Korea*

—Clinical analysis and treatment results in 61 cases—

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A clinical analysis was made of 61 cases of multiple myeloma diagnosed between January 1976 and June 1984 at Seoul National University Hospital using the criteria of the Southwest Oncology Group.

The following observations were made.

1) The major clinical problems at initial presentation were bone pain(52%), anemia(20%), renal impairment(11%), and infection(10%).

2) Clinical stages at presentation were stage I, 11%; stage II, 8%; and stage III, 81% of patients. Three(5%) of the patients in stage II and 18(31%) in stage III showed renal impairment with a serum creatinine ≥ 2.0 mg/dl.

3) Combination chemotherapy produced a response rate of 29% with melphalan and prednisone, and 40% with M2 protocol(among 14 and 20 evaluable patients respectively). Both regimens showed statistically significant survival difference between responders and non-responders($p<0.01$).

4) The median survival of all patients was 13 months.

5) Age, calcium level, creatinine level, and performance status were important prognostic factors on survival.

Key Words: *Multiple myeloma, Melphalan and prednisone, M2 protocol*

INTRODUCTION

Multiple myeloma is one of the most common plasma cell neoplasms and mainly involves bone and bone marrow. It is not an uncommon disease in Korea. Previous studies in Korea included only small numbers of cases. In 1972 an initial statistical analysis of 28 cases was presented at the Korean Hematology Meeting[1]. A second report was made at the 4th International Hematology Meeting of Asia and Pacific Area[2]. Additional studies concentrating on the M-protein were reported at the Korean Hematology Meeting in 1983[3]. As of this writing, there has been no Korean report on the results of chemotherapy.

We, therefore, analyzed the clinical features and chemotherapeutic results of 61 patients with multiple myeloma who were diagnosed between January 1976 and June 1984 at Seoul National University Hospital.

MATERIALS AND METHODS

Between January 1976 and June 1984, 61 consecutive patients were diagnosed as having multiple myeloma at Seoul National University Hospital. The diagnosis was established according to the criteria of the Southwest Oncology Group (SWOG)[4]. The patients were clincally staged using

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**Presented at the 36th Annual Meeting of the Korean Association of Internal Medicine, Seoul, Korea, October 1984*

Supported in part by Seoul National University Hospital

the system developed by Durie and Salmon[5].

Twenty one patients were treated with melphalan and prednisone (MP, Table 1), and 25 patients with the M2 protocol (Table 2)[6]. An objective response was defined as a reduction of 50% or more in serum M-protein concentration or in urine 24 hour light chain excretion[7]. This protein response must be accompanied by normal serum calcium, serum albumin above 3 g/dl, and no progression of skeletal disease. Determination of treatment effect was limited to patients who had received at least 2 cycles of chemotherapy, and whose M-protein levels had been continuously monitored. Remission duration was defined as the period from the day when the M-protein concentration decreased to less than 50% of the pretreatment value to the day when it doubled from the lowest value obtained during the remission period. Survival curves were calculated from the start of the therapy using the Kaplan-Meier product limit method, and the log-rank test was used for the comparison of survival curves.

Table 1. Schedule of MP Chemotherapy Regimen

Melphalan	0.1 mg/kg	p.o. day 1–7	Repeat cycle
Prednisone	1 mg/kg	p.o. day 1–7	Every 4 weeks

Table 2. Schedule of M_2 Protocol

Vincristine	0.03mg/kg	i.v. day 1	
Melphalan	0.1 mg/kg	p.o. day 1–7	Repeat cycle
Cyclophosphamide	10 mg/kg	i.v. day 1	Every 4 weeks
BCNU	0.5 mg/kg	i.v. day 1	
Prednisone	1 mg/kg	p.o. day 1–7	

RESULTS

1. Clinical Features

Patient ages ranged from 15 to 81 years (median age: 54 years). Fifty five (90%) of the 61 patients were 40 years or older. The male to female ratio was 2.8: 1 (Table 3).

Bone pain (52%) and anemia (20%) were the most common clinical problems at the time of initial presentation. Eleven percent of the patients presented with renal problems including acute or chronic renal failure and 10% with infection manifested by pneumonia, urinary tract infection or sepsis (Table 4).

Twelve cases (20%) showed plasmacytomas on biopsy of bone or soft tissue. Thirty nine cases (65%) showed bone marrow plasmacytosis which occupied more than 10% of all the nucleated cells.

Protein electrophoresis and immunoelectrophoresis of serum and urine was done in 55 patients, and the M-protein spike was demonstrated in 50 patients. IgG was the most common type accounting for 25 cases (50%), IgA for 14 cases (28%), IgD for 4 cases (8%), and light chain only for 7 cases (14%). The ratio of kappa light chain to lambda light chain was 1.1 : 1. In 15 patients (25%), concentration of normal immunoglobulins was reduced. Three patients presented as solitary plasmacytoma of bone, 1 as an extramedullary plasmacytoma of the maxillary sinus, and 1 as a nonsecretory myeloma.

Forty one (68%) of the 61 patients showed osteolytic bone lesions, and 4 (6%) showed osteoporosis only on skeletal survey. In 16 patients (26

Table 3. Age and Sex Distribution of Patients at Diagnosis

Age (yr)	Male	Female	Total
< 40	6	–	6 (10%)
40 – 49	10	1	11 (18%)
50 – 59	18	7	25 (41%)
60 – 69	8	7	15 (25%)
⩾ 70	3	1	4 (6%)
Total	45 (74%)	16 (26%)	61 (100%)

Table 4. Major Problems at Initial Presentation

Problems	No. of pt. (%)
Bone pain	32 (52%)
Anemia	12 (20%)
Renal dysfunction	7 (11%)
Infection	6 (10%)
Root pain	2 (3%)
Hemorrhagic manifestation	1 (2%)
Miscellaneous	1 (2%)

Table 5. Initial Skeletal Roentgenographic Findings

Findings	No. of pt. (%)
Normal	16 (26%)
Osteoporosis	4 (6%)
Lytic bone lesions	17 (28%)
Advanced lytic bone lesions	24 (40%)

%) the bone X-ray revealed no abnormalities (Table 5).

Nineteen patients (31%) had hemoglobin values over 10 g/dl, and 25 (41%) below 8.5 g/dl. Nine (15%) showed serum calcium levels over 13.0 mg/dl, and 4 (6%) between 11.0 mg/dl and 13.0 mg/dl. Those with serum creatinine level equal to or greater than 2.0 mg/dl were 21 (34%), and those below 1.4 mg/dl were 32 (52%).

Seven patients (11%) were classified as stage I, 5 (8%) as stage II, and 49 (81%) as stage III. Three (5%) of the patients in stage II and 18 (30%) in stage III showed renal impairment with a serum creatinine ≥2.0 mg/dl (Table 6).

Table 6. Initial Clinical Stage of Patients

Stage		No. of pt. (%)
Stage I	A	7 (11%)
	B	0 (0%)
Stage II	A	2 (3%)
	B	3 (5%)
Stage III	A	31 (51%)
	B	18 (30%)

Table 7. Results of Chemotheraphy

	MP	M_2
1. No. of pt.	21	24
2. Response	4/14 (29%)	8/20 (40%)
3. Median response duration	6 months	20 months
4. Side effects		
Leukopenia	5/14 (36%)	8/20 (40%)
Thrombocytopenia	0/14	2/20 (10%)
Nausea & vomitting	0/14	2/20 (10%)

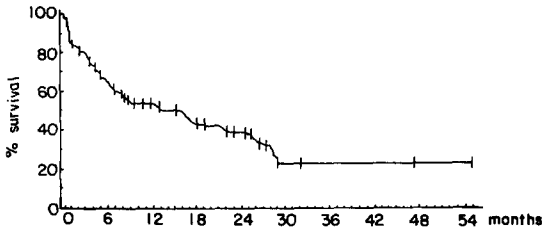

Fig. 1. *Survival curve of all patients.*

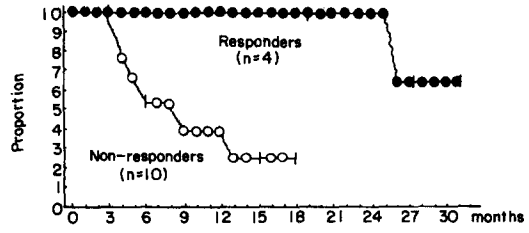

Fig. 2. *Survival curves by response to MP regimen.*

2. Results of Treatment

Out of 21 patients who were treated with MP therapy, 14 were evaluable. Among them, 4 patients (29%) achieved objective responses, and the median duration of response was 6 months. Twenty out of 24 patients who received the M2 protocol were evaluable. Objective responses were obtained in 8 patients (40%), and the median duration of response was 20 months. Chemotherapy related toxicity was not uncommon, but usually self-limiting and no treatment-related deaths were observed (Table 7). The median survival of the overall patients was 13 months (Fig. 1). There were statistically significant survival differences between responders and nonresponders to MP therapy (30 months vs 8 months, $p<0.001$, Fig. 2), and to M2 protocol treatment (28 months vs 16 months, $p<0.01$, Fig. 3).

Age, calcium level, creatinine level and performance status were important prognostic factors on survival. Patients with IgA M-protein survived longer than those with light chain only or IgG M-protein (Table 8).

Thirteen patients died at our hospital. The causes of death were as follows; acute renal failure with pulmonary edema in 6, sepsis in 4, intractable bleeding in 2, and airway obstruciton in 1.

DISCUSSION

The annual incidence of multiple myeloma in the U.S.A. is 3 per 100,000 population, with a peak occurrence at ages 50 to 70 year[8]. This disease rarely occurrs before 40 years of age, and is slightly more common in males than in females.

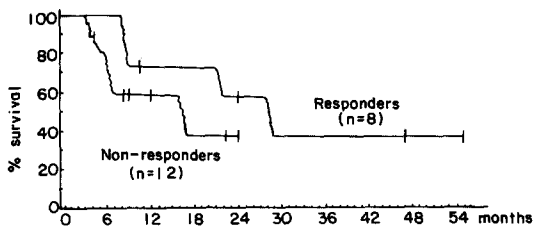

Fig. 3. *Survival curves by response to M_2 protocol.*

Table 8. Survival According to Various Prognostic Factors

Factors		Median survival	P value
1. Age	≤ 50	25 months	< 0.001
	> 50	8 months	
2. Calcium	≤ 11.0 mg/dl	12 months	< 0.001
	> 11.0 mg/dl	8 months	
3. Creatinine	< 2.0 mg/dl	17 months	< 0.001
	≥ 2.0 mg/dl	6 months	
4. Performance	1, 2	12 months	< 0.001
	3, 4	8 months	
5. M-protein	IgA	17 months	
	Light chain only	8 months	< 0.05
	IgG	5 months	< 0.001

The incidence in Korea is unknown, but it comprises about 0.3% of all malignancies in Korea[9]. In this study, the peak incidence was at ages 50 to 59 years with a median of 54 years, and only 6 patients (10%) were younger than 40 years of age. The male to female ratio was 2.8 : 1.

Patients with myeloma have variable clinical manifestations. Bone pain is present in 68% of patients at diagnosis, anemia in 62%, and renal problems in 50%[10]. Renal problems include proteinuria, tubular dysfunction, urinary tract infection, acute renal failure and chronic renal failure. Infection is frequent due to an abnormal immune system. The overall incidence is 1.46 infectious episodes per patient-year, and nearly 70% of patients with myeloma die as a result of infection[11]. The two months immediately following the start of initial chemotherapy was the most hazardous period. In this study, the most common clinical problems at initial presentation were bone pain (52%) and anemia (20%). Other problems include acute or chronic renal failure (11%), and infection (10%). Renal failure and infection were the most common causes of death.

Kyle et al. reported the relative distribution of immunoglobulin classes by serum and/or urine immunoelectrophoresis[10]. It was IgG 59%, IgA 23%, IgD 1%, and light chain only 17%. In this study, it was IgG 50%, IgA 28%, IgD 8%, and light chain only 14%.

There are many prognostic factors influencing patient survival, among which serum creatinine level is considered the most important. Other prognostic factors include performance status, hemoglobin level, serum albumin and calcium level, degree of osteolytic lesion, and amount of M-protein. The clinical staging system was developed on these parameters[5]. Santoro et al. reported that the median survival from diagnosis was 48 months for stage I, 41 months for stage II and 23 months for stage III[12]. The median survival of patients with normal renal function was 35 months compared to 7 months for those with renal impairment. Response to chemotherapy is another important prognostic factor on patient survival [12,13]. Patients who obtained objective responses survived much longer than those who did not. In this study, age, calcium level, creatinine level, performance status, and response to chemotherapy were found to be important prognostic factors. The median survival of patients with myeloma has been reported as 2 to 3 years[8]. In this study the median survival of patients was 13 months. This poor result might be explained by the fact that the majority of patients in this study were in advanced stages at the initial presentation.

Treatment of multiple myeloma is composed of general supportive care and chemotherapy. Supportive care aims to preserve ambulation and mobility, control pain and avoid dehydration. Management of complications, i.e., control of hypercalcemia, skeletal destruction, infection and renal dysfunction is also an important aspect of supportive measures. However, definitive treatment of myeloma calls for chemotherapy. Current drugs shown to be effective as a single agent include alkylating agents (melphalan, cyclophosphamide, chlorambucil), nitrosoureas, procarbazine, and doxorubicin, each of which has a remission rate of about 20-50%[14~16]. To improve the remission rate and to prolong the survival time many combination chemotherpay regimens were

investigated. One of the most commonly employed regimens is a combination of melphalan and prednisone (MP), which showed a remission rate of 48% and remission duration of 24 months [13]. The best reported results of combination chemotherapy are those based upon the M2 protocol developed by investigators at Memorial Sloan Kettering Cancer Center[6]. This regimen combines melphalan, prednisone, cyclophosphamide, vincristine, and BCNU. A remission rate of 78–87% and median survival of 38–50 months were reported[6,17]. The Eastern Cooperative Oncology Group compared this M2 protocol with MP therapy in a randomized study. Objective responses were seen in 74% of the patients receiving the M2 regimen, and in 53% of those receiving the MP regimen. But the median survival did not differ at 33 and 29 months, respectively[18]. In our study, the MP regimen produced a 29% remission rate, and the M2 protocol 40%. This lower remission rate could be explained by the large numbers of patients in advanced disease in our stydy. When patients fail to respond to initial therapy or relapse after responding to first line drugs, second-line treatment may be tried. A combination chemotherapy with BCNU and doxorubicin was shown to have a response rate of 54% in relapsed patients [19]. We treated 5 patients, 4 initial nonresponders and 1 relapsed patient, with BCNU and doxorubicin, but none of them responded. We think that more systematic and continous studies are required on this subject in Korea.

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