Renal Dysfunction in Multiple Myeloma

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This study aims to determine the clinical factors that may affect renal function and patient survival in 82 multiple myeloma patients. The patients were divided into 3 groups according to their renal function during the initial 8 weeks after diagnosis: Group I, 54 patients with serum creatinine (S-Cr) <177 $\mu\text{mol/L}$; Group II, 11 with S-Cr $\geq 177 \mu\text{mol/L}$ and receiving no dialysis; Group III, 17 undergoing dialysis treatment. Clinical status at diagnosis, subsequent renal function and patient survival were compared. Bence Jones proteinuria (BJP) was found in all patients in Groups II and III, compared to 67% of patients in Group I ($p < 0.05$, I vs II or III). Hypercalcemia, hyperuricemia and intravenous administration of contrast medium, together with BJP each constituted independent risk factors of renal dysfunction. The incidence of hypercalcemia in Group II was significantly higher than in the other 2 groups. Patient survival was 26.8 ± 23.7 months in Group I, 8.1 ± 10.3 in II and 12.1 ± 16.6 in III ($p < 0.05$, I vs II or III). Renal function and patient survival depended on the initial renal function. Renal function was likely compromised in the presence of BJP. (Internal Medicine 34: 364–370, 1995)

Key words: renal failure, prognosis, Bence Jones proteinuria, hypercalcemia, contrast medium

Introduction

Multiple myeloma (MM) is a disease characterized by the increased production of monoclonal immunoglobulin components, as a result of malignant plasma cell proliferation. Renal dysfunction constitutes one of the major complications of MM, and occurs in 55% of patients (1). Renal dysfunction contributes to 21% of deaths in MM patients, and is the second most common cause of death next to infectious diseases (1, 2). The life expectancy of MM patients averages 20 months, and renal dysfunction significantly adds to the poor one- and five-year survival rates of 66 and 18% (1, 3–5). Since renal dysfunction complicating MM was considered irreversible, the indication of dialysis treatment was questionable in MM patients with renal failure (6). However, due to recent advances in chemotherapy, many patients have shown recovery of renal function by active treatment schemes including plasmapheresis and dialysis (7–16). The life expectancy of patients with reversed renal failure was found to be longer than those without reversal (12, 13). Some patients with irreversible renal failure however were able to be maintained on long-term dialysis for over 12 months (8, 13, 17). These reports clearly demonstrate the legitimacy of dialysis treatment of renal dysfunction.

The pathogenesis of renal dysfunction in MM patients is varied. Dysfunction caused by myeloma protein includes my-

eloma kidney, Faconi syndrome, light chain deposition disease and amyloid nephropathy. Renal dysfunction can also be induced by other pathologic factors associated with MM, such as hypercalcemia, hyperuricemia, hyperviscosity syndrome, and urinary tract infection (pyelonephritis) due to the propensity to infection. Other forms of renal dysfunction include obstructive renal impairment due to myeloma cell infiltration or calculus, acute tubulorrhexis due to dehydration and contrast medium, and tubulo-interstitial nephritis due to nonsteroidal anti-inflammatory drugs (NSAIDs) (18). Renal dysfunction can occur at any time during the course. However, the clinical sequelae of renal dysfunction found before and after the diagnosis of MM, and its effects on prognosis have not yet been studied. We divided MM patients according to their renal function during the eight weeks after the diagnosis, and followed the time course of renal dysfunction and patient survival in each group.

Patients and Methods

Patients

Eighty-two out of the 116 consecutive MM patients, who were admitted to Kitasato University Hospital from July 1971 through October 1992, and were followed up to the time of their physical or renal death, formed the basis of the present study (Table 1).

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Table 1. Patient Profile and Clinical Laboratory Data on Admission in Multiple Myeloma Patients of Groups I, II and III*

	Group I	Group II	Group III	Total
No. of patients	54 (66%)	11 (13%)	17 (21%)	82
Age at diagnosis (yrs)	64.2±10.3	61.5±12.4	63.6±12.1	63.7±10.9
Male/female	28/26	7/4	12/5	47/35
Hemoglobin (g/dL)	9.25±2.07	9.39±2.38	8.68±2.06	9.15±2.10
Rouleaux formation (%)	32 (59%)	3 (27%)	6 (35%)	41 (50%)
Total protein (g/L)	93.4±26.9 ^a	79.7±30.5	71.4±16.0	86.7±27.2
Serum albumin (g/L)	36.4±7.2	33.9±7.0	38.0±7.3	36.4±7.2
Corrected Ca ⁺⁺ (mmol/L)**	2.32±0.28	2.91±0.42 ^b	2.47±0.40	2.43±0.38
Serum creatinine (μmol/L)	82±26	198±133 ^c	821±363 ^e	251±341
Serum urea nitrogen (mmol/L)	6.6±2.7	10.9±5.5 ^d	29.9±10.6 ^e	12.1±10.9
Serum uric acid (μmol/L)	373±114	431±116	550±210 ^f	416±155
Myeloma cells in bone marrow (%)	36.0±22.9	61.7±20.0 ^b	48.9±31.2	41.9±25.8

*Patients were divided into three groups according to their renal function at the time of diagnosis (see text).

**Corrected serum Ca⁺⁺ (mmol/L) = serum Ca⁺⁺ level measured (mmol/L) – 1/40 • serum albumin (g/L) + 1. ^ap<0.01 vs Group III; ^bp<0.01 vs Group I & Group III; ^cp<0.05 vs Group I; ^dp<0.01 vs Group I; ^ep<0.01 vs Group I & Group II; ^fp<0.01 vs Group I, p<0.05 vs Group II.

Methods

The above 82 patients were divided into three groups according to their renal functional status at the time when MM was diagnosed, or within 8 weeks thereafter: Group I, 54 patients whose serum creatinine (S-Cr) levels were less than 177 μmol/L; group II, 11 patients who had S-Cr level of 177 μmol/L or higher, but who did not require dialysis; and group III, 17 patients who were submitted to dialysis treatment. The initial 8 weeks after diagnosis of MM were selected as appropriate for patient grouping, since most early complications were included within the time period and the clinical course of MM became generally stabilized into a sustained steady state. The three groups were retrospectively compared for the following clinical parameters:

– *Age at diagnosis and sex*

– *Complete blood count (CBC)* was determined using Coulter Counter Model-S (Coulter, Florida, USA), Technicon Hemalog 8 (Technicon, New York, USA), Technicon H-6000 (Technicon), Sysmex E-4000 (Toa Iyo Denshi, Japan) and Coulter STKS (Coulter).

– *Red cell morphology* and the presence of *rouleaux formation* were determined by microscopically studying blood smears.

– *Total serum protein (TP), serum albumin (Alb), serum urea nitrogen (SUN), S-Cr, uric acid (UA) and corrected calcium (Ca)* levels were determined using Hitachi 736-10 (Hitachi, Japan) and Hitachi 7150 autoanalyzer (Hitachi). Corrected Ca level (mmol/L) was estimated from measured Ca level (mmol/L) – Alb level (mmol/L) +1, according to Payne et al (19). Serum uric acid levels of 595 μmol/L (10 mg/dL) or above were defined as hyperuricemia, and corrected Ca levels of 3.0 mmol/L (12.0 mg/dL) or above, as hypercalcemia.

– *24-hour urine protein level* (average of three consecutive days), was determined with sulfosalicylic acid. The amount of *urine albumin* was estimated from urine total protein multiplied

by the albumin ratio obtained with electrophoresis, and graded into four degrees: less than 0.15 g/day, 0.15 to less than 1.0, 1.0 to less than 3.5, and 3.5 or more.

– *Bence Jones proteinuria (BJP)* was immunoelectrophoretically determined. Urinary BJP level was obtained by multiplying urine total protein with the excretory ratio of the monoclonal component.

– *Serum and urinary myeloma proteins* were determined by immunoelectrophoresis, and categorized as: BJP only, IgG+BJP, IgG only, IgA+BJP, IgA only, IgD+BJP, IgD only, and IgG+IgA+BJP.

– *The myeloma cell ratio in the bone marrow* was measured using smears obtained by sternal or iliac tap.

– *Whole body skeletal survey by X-ray* was performed to look for the presence of MM-associated bone lesions, such as osteoporosis, osteolysis and pathologic fracture. ‘Punched out’ lesions were included in osteolysis.

– *Treatment of MM*: chemotherapy and types of agents used; radiotherapy, dosage and site; and plasmapheresis were evaluated.

– *Patient survival rate* was obtained as the number of survivors/total patient number.

– *The number of dialyzed patients and the initiating cause.*

– *Time lapse between the diagnosis of MM and the start of dialysis, the duration of dialysis, the survival time on dialysis, and the direct causes of death* were determined.

– *Potential triggers for renal dysfunction.* The incidence of renal dysfunction in cases who had triggering factors such as NSAIDs, hyperuricemia, hypercalcemia, contrast medium, and cepheids and diuretics was studied. The triggers which were present during the 16 weeks (8 weeks before to 8 weeks after) around the time of MM diagnosis were searched, and the simultaneous presence or absence of renal dysfunction was determined. In patients who had multiple triggers, they were

separately treated.

Statistical analysis

The significance level of differences among the three groups was assessed with analysis of variance or χ^2 test. The differences among individual Kaplan-Meier's survival curves were calculated using Cox-Mantel's test. *P* value of less than 0.05 was defined as significant.

Results

Clinical profile

The average age at diagnosis of 82 MM patients was 63.7 ± 10.9 years (Table 1). The male to female ratio was 47 to 35. No significant intergroup differences in average age or male to female ratio were found among Groups I, II and III.

Laboratory findings on admission

CBC, blood chemistry and the findings of bone marrow (Table 1)

No significant intergroup differences in hemoglobin level and rouleaux formation were observed. The serum total protein level in Group I (93.4 ± 26.9 g/L) was significantly higher than that of Group III patients ($p < 0.01$). All groups showed comparable levels of serum albumin. The corrected Ca level of Group II (2.91 ± 0.42 mmol/L) was significantly higher compared with Groups I and III ($p < 0.01$). The serum Cr level in Group I patients (82 ± 26 μ mol/L) was, by definition, significantly lower compared with Groups II and III (198 ± 133 μ mol/L and 821 ± 363 μ mol/L, respectively); the same was true for the urea nitrogen levels. The serum uric acid level in Group III alone fell in the range of hyperuricemia (550 ± 210 μ mol/L). The % myeloma cells in the bone marrow of Group II ($61.7 \pm 20.0\%$) was significantly increased compared to Group I ($36.0 \pm 22.9\%$, $p < 0.05$).

Urinary excretion of albumin and myeloma protein (Table 2)

The average total urinary protein in 70 patients studied was 1.75 ± 2.65 g/day, with no significant intergroup variation among Groups I, II and III. Most patients had no detectable or only low levels of urinary albumin (the average level in 59 patients was 0.27 ± 0.76 g/day). Only three (1 case in Group I and two in Group III) patients excreted 1.0 g/day or more albumin in the urine out of 59 cases studied (5.1%). One of these three (Group III) had nephrotic syndrome and excreted an average of 5.6 g/day albumin in the urine. No significant differences in the amount of urinary myeloma protein were found among the three groups. However, the incidence of urinary BJP-positive patients in Group I (36 of 54 cases or 67%) was significantly less compared with the positivity ratio (100%) in Groups II and III.

The incidence of serum myeloma proteins (Fig. 1)

The percentage of M proteins found in the sera were in the following descending order: BJP, IgG, IgA, IgD and IgG+IgA. The same held true with M proteins in the urine (data not shown). In Groups II and III, BJP alone was most frequently observed; also in the remaining M protein-positive samples BJP was always found in combination with other paraproteins, in contrast to the findings of Group I. In addition, Group III was unique due to a significantly higher incidence of IgD+BJP (29.4%).

Skeletal bone survey by X-rays (Table 3)

Abnormalities in X-ray were observed in 60 of 81 cases (74.1%), including all 11 cases (100%) in Group II. The % osteoporosis in Group I (60.0%) was significantly higher than that in Groups II or III. On the other hand, the incidence of osteolytic lesion or pathologic fracture was comparable among the three groups.

Treatment

Seventy-two of 82 cases (87.8%) were, at some time point

Table 2. Urinary Protein Excretion on Admission

	Group I	Group II	Group III	Total
1) Urinary protein excretion (g/day)	1.47 ± 2.95 [44]	2.00 ± 1.61 [10]	2.38 ± 2.24 [16]	1.75 ± 2.65 [70]
2) Urinary albumin excretion (g/day)	0.15 ± 0.25 [35]	0.29 ± 0.27 [9]	0.54 ± 1.44 [15]	0.27 ± 0.76 [59]
<0.15	[24] (68.6%)	[4] (44.4%)	[9] (60.0%)	[37] (62.7%)
0.15 to <1.0	[12] (28.6%)	[5] (55.6%)	[4] (26.6%)	[19] (32.2%)
1.0 to <3.5	[1] (2.9%)	[0]	[1] (6.7%)	[2] (3.4%)
3.5 $\leq$	[0]	[0]	[1] (6.7%)	[1] (1.7%)
Unknown	[19]	[2]	[2]	[23]
3) Urinary excretion of myeloma protein (g/day)	1.28 ± 2.88 [35]	1.57 ± 1.66 [9]	1.76 ± 2.09 [15]	1.45 ± 2.52 [59]
Negative for BJP	[18] (33%)	[0]	[0]	[18] (22%)
Positive for BJP	[36] (67%)	[11] *(100%)	[17] *(100%)	[64] (78%)

[] No. of patients; () Incidence in each group of patients; BJP: Bence Jones protein. * $p < 0.05$ vs Group I by chi-square test. ** $p < 0.01$ vs Group I by chi-square test.

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Fig. 1. Myeloma proteins detected in the sera of the patients, who were divided into three groups according to their renal function at the time of diagnosis. () No. of patients, BJP: Bence Jones protein. * $p < 0.05$ vs Group I, ** $p < 0.01$ vs Group I.

during the course, submitted to one or more courses of chemotherapeutic agents, including 49 cases in Group I (90.7%), 11 in Group II (100%) and 12 in Group III (70.6%) (data not shown). Combinations of agents employed were MP (melphalan + prednisolone), MOP (melphalan + vincristin + prednisolone), COP (cyclophosphamide + vincristin + prednisolone), or VCAP + Sumiferon® (vincristin + cyclophosphamide + doxorubicin hydrochloride + prednisolone + interferon). Radiation, in combination with chemotherapy, was administered in 9 patients (11.0%) who had severe bone lesions, these were 5 cases in Group I, and 2 each in Groups II and III. The total dosage given varied from 3,000 to 44,500 mGy (300 to 4,450 rad). Plasmapheresis was performed in 11 patients with hyperviscosity syndrome (13.4%), including 8 cases in Group I and 3 in Group III.

Fig. 2. Kaplan-Meier's patient survival curve. Patients were divided into three groups according to their renal function at the time of diagnosis. -- Group I (n=54), — Group II (n=11), Group III (n=17), — All patients (n=82). $p < 0.01$; Group I vs Group II & III by Cox-Mantel's test.

Patient survival (Fig. 2)

The survival curves in both Groups II and III were significantly different from that in Group I ($p < 0.01$). The average survival time was 26.8 ± 23.7 months for Group I, which was significantly longer compared with Group II (8.1 ± 10.3) and Group III (12.1 ± 16.6 ; $p < 0.05$). Group II patients showed the poorest prognosis, with no survivors after 3 years.

The number of dialyzed patients and the triggers initiating dialysis (Table 4)

Dialysis was initiated in 19 patients (23.2%), all of whom were treated with hemodialysis (HD). The 19 patients included all 17 in Group III and 2 in Group I. No Group II patients were submitted to HD. In the two Group I cases, HD was started two years after the diagnosis of MM was made. Discontinuance of HD due to recovery of renal function occurred in only two cases in Group III. The triggers initiating dialysis were hyperuricemia, intravenous injection of contrast medium, hypercalcemia, combined administration of cephem antibiotics and diuretics, inappropriate use of NSAIDs, etc.

Table 3. Findings in Bone X-P

	Group I	Group II	Group III	Total
Normal X-P	14 (25.9%)	0	7 (43.8%)	21 (25.9%)
Abnormal X-P	40 (74.1%)	11 (100%)*	9 (56.2%)	60 (74.1%)
<Abnormal Findings>				
Osteoporosis	24 [60.0%]**	2 [18.2%]	1 [11.1%]	27 [45.0%]
Osteolytic lesion	23 [57.5%]	6 [54.5%]	6 [66.6%]	33 [55.0%]
Pathological fracture	18 [45.0%]	5 [45.6%]	3 [33.3%]	26 [43.3%]
Not studied	0	0	1	1

() Incidence of each category (no. of patients belonging to each category/no. of total cases).

[] Incidence of each finding in each category (no. of patients with each lesion/no. of total patients with bone X-P abnormality). * $p < 0.01$ vs Group III. ** $p < 0.01$ vs Group III, $p < 0.05$ vs Group II.

Table 4. Triggering Factors for the Initiation of Hemodialysis Treatment in Multiple Myeloma Patients

	Group I 54 cases	Group II 11 cases	Group III 17 cases	Total 82 cases
No. of the patients who required hemodialysis treatment	2	0	17 [2]	19 [2]
<Triggering factors>				
Hyperuricemia*	—	—	4	4
Contrast medium	—	—	3 [1]	3 [1]
Hypercalcemia**	—	—	2	2
Cephems + Diuretics	1	—	1	2
Cephem + Dehydration	—	—	1	1
NSAIDs	1	—	1 [1]	2 [1]
Dehydration	—	—	1	1
Amyloid nephropathy	—	—	1	1
Congestive heart failure	—	—	1	1
Obstructive jaundice	—	—	1	1
Unknown	—	—	1	1

*Serum uric acid level $\geq 595 \mu\text{mol/L}$. **Corrected serum calcium $\geq 3.0 \text{ mmol/L}$.

[] No. of patients who recovered functionally and became free from the need for dialysis treatment.

Clinical course of 19 dialyzed patients (Fig. 3)

The two Group I patients who developed renal failure two years after MM was diagnosed, remained on dialysis until their death due to heart failure or cerebral hemorrhage. In two of the 17 cases in Group III, in whom renal failure was due to either contrast medium or NSAID, dialysis was discontinued within two weeks after initiation. In these two cases, although their serum creatinine levels after discontinuation of the dialysis treatment remained stable at $133 \mu\text{mol/L}$ and $239\text{--}309 \mu\text{mol/L}$, respectively, they died of septicemia or heart failure after more than 2 years. Thirteen of the 15 patients who were maintained on chronic dialysis died of extra-renal complications such as hemorrhage, infections, heart failure and obstructive jaundice within 12 months after initiating hemodialysis. One of the remaining two patients died after 60 months, and the last case was still alive 6 months after the initiation of dialysis, at the time of this writing.

The potential triggers of renal dysfunction (Table 5)

The incidence of the potential triggers leading to renal dysfunction around the time of MM diagnosis were, in descend-

Fig. 3. Survival time and causes of death in dialyzed patients. Patients were divided into three groups according to their renal function at the time of diagnosis. — Without dialysis treatment, ■ With dialysis treatment. Causes of death: 1) congestive heart failure, 2) hemorrhage, 3) infection, 4) obstructive jaundice, 5) ileus.

Table 5. Frequency Numbers and Incidence of Renal Dysfunction in the 82 Multiple Myeloma Patients Exposed to the Potential Triggering Factors

Triggering factors	No. of exposed patients	Incidence of exposure	Percentage of the patients		Total (%)
			Group II	Group III	
Total of the following five factors	59	83	9 (10.8%)	11 (13.3%)	20 (24.1%)
NSAIDs	27	33	2 (6.1%)	1 (3.0%)	3 (9.1%)
Hyperuricemia	16	16	1 (6.3%)	4 (25.0%)	5 (31.3%)
Hypercalcemia	14	14	5 (35.7%)	2 (14.3%)	7 (50.0%)
Contrast medium	10	13	0	3 (23.1%)	3 (23.1%)
Cephems + Diuretics	7	7	1 (14.3%)	1 (14.3%)	2 (28.6%)

ing order, NSAIDs, hyperuricemia, hypercalcemia, contrast medium and inappropriate use of cepheims and diuretics. Total occurrence of renal dysfunction in 59 patients with MM who were exposed to any of the above factors was 20 (24.1%). Incidence of renal dysfunction induced by individual factors were, in descending order, hypercalcemia, hyperuricemia, contrast medium, inappropriate use of cepheims and diuretics, and NSAIDs.

Discussion

In the present study, the survival of patients who had significant renal dysfunction within 8 weeks of diagnosis of MM, whether they were submitted to dialysis (Group III) or not (Group II), was shown to be compromised to less than half compared with patients without significant renal dysfunction (Group I). These results may indicate that the degree of renal impairment within 8 weeks of MM diagnosis can predict the ultimate prognosis of these patients. Regarding the renal functional prognosis, 14 of 17 patients who initially required dialysis treatment within 8 weeks after diagnosing MM remained on dialysis until death. In contrast, of the 54 Group I patients and 11 Group II, only 2 Group I patients subsequently required dialysis treatment two years after the diagnosis of MM. Two patients in Group III, who were taken off dialysis within four weeks of initiation, subsequently had an improved renal function and enjoyed longer survival than the rest who remained on dialysis treatment. Accordingly, initial renal impairment, which may be relevant to patient survival, also likely determines the long-term renal functional status.

All Group II patients, who were often hypercalcemic, showed bone abnormalities in skeletal survey by X-rays, and 90% of them were graded as Durie's stage III, which was reported to have a poor life expectancy (20). The finding of a high percentage (an average of 61.7%) of myeloma cells in the bone marrow smear of Group II patients may mirror the rapid proliferation of these cells in the marrow, and may have caused hypercalcemia resulting in renal dysfunction. The cause of hypercalcemia in MM has been reported to be associated with soluble factors such as osteoclast activating factor (OAF) (21). Other factors may also be involved, but they are beyond the scope of this study. The incidence of hypercalcemia (corrected serum Ca ≥ 3.0 mmol/L) was 5 cases in Group II (45%) and 2 in Group III (12%), with none in Group I. Hypercalcemia has been reported to complicate 30% of MM cases (1, 5). Hypercalcemia and/or Bence Jones proteinuria were shown to explain the renal failure in 97% of MM patients (22). Durie and Salmon (20) reported an average life expectancy of 6 months for MM patients with serum calcium concentrations of 3.0 mmol/L or above. It was significantly shorter ($p < 0.01$) than the average life expectancy of 52 months for patients with serum calcium concentrations lower than 3.0 mmol/L. Alexanian et al (4) also reported the average duration of remission of MM in patients with hypercalcemia to be significantly shorter than in those without such complication. In the present study, the mean survival in Group II patients averaged around 8 months, but the causes of

death were varied, including 3 cases each of cardiac dysfunction and infection, 2 of digestive tract bleeding, and one each of cerebral hemorrhage and pulmonary emboli of bone marrow tissue. The remaining Group II patient was alive nearly 2 years after the diagnosis. Further study is necessary to determine whether the poor prognosis of MM patients with renal dysfunction, who did not require dialysis but tended to complicate hypercalcemia (Group II) was due to the rapid multiplication of tumor cells or to hypercalcemia-induced cardiac failure.

At the time of diagnosis of MM, all 17 cases in Group III had SUN level ≥ 14.3 mmol/L (40 mg/dL), and serum Cr ≥ 265 μ mol/L (3.0 mg/dL). In 10 cases (59%), the serum Cr was ≥ 707 μ mol/L (8.0 mg/dL). In other words, it may safely be said that nearly all Group III cases had end-stage renal failure at the time of diagnosis. While the serum uric acid level in Group III was as high as 550 μ mol/L, the % myeloma cells in the bone marrow smear was not significantly different from that of Group I. Although the production rate of uric acid was not measured, the above results indicated that hyperuricemia in Group III was secondary to impaired renal excretion rather than to the increased destruction of rapidly multiplying myeloma cells.

All patients in Groups II and III had serum BJP, while only 67% of Group I patients were positive for BJP ($p < 0.05$ I vs II or III). Although no clear correlation was observed between the amount of BJP excreted in the urine and the degree of renal dysfunction, it is likely that renal impairment may be related to BJP in a non-dose-dependent manner. Regarding the M protein types, 14 of the BJP-positive patients (61%) and 6 of the IgD-positive patients (75%) belonged to Groups II and III. This finding is compatible with that of Jancelewicz et al (23), who reported that BJP and IgD are the most common types of M proteins found in patients with renal dysfunction. Renal impairment in BJP-positive patients is likely due to the formation of numerous tubular casts in the so-called myeloma kidney, leading to tubular dysfunction. The BJP found together with IgD is more frequently of λ chain-type, compared with its incidence found with IgG or IgA (23, 24), which suggests the possible involvement of λ chain in the genesis of IgD-related renal impairment. According to an interesting paper recently published by Solomon et al (25), a particular subtype of BJP was shown to be highly nephrotoxic or amyloidogenic. They injected BJP, obtained from MM patients whose serum Cr concentrations equaled or exceeded 168 μ mol/L (1.9 mg/dL), into mouse peritoneum, and demonstrated an appearance of histopathologic changes in murine kidneys comparable to the original human pathology, whereas the incidence of BJP deposition was much smaller when mice were injected proteins obtained from patients with serum Cr concentrations below 168 μ mol/L.

Potential triggers for initiating dialysis were found in 18 of the 19 patients who were submitted to dialysis treatment. The triggering factors found in this study do not necessarily agree with the tendency in recent years, which has been a decrease in the use of contrast medium and an increase in infection, hypercalcemia and dehydration (12, 13). The reason may be relevant to the prolonged observation period in this study

extending over the past twenty years.

The major triggers causing renal dysfunction in Group II patients, which were observed around the time of MM diagnosis, were hypercalcemia and NSAIDs, with a combination of the two in 2 cases. They had severe bone lesions leading to hypercalcemia and bone pain; renal dysfunction was triggered by the inadvertent use of analgesics prescribed for the bone pain.

Ten of 13 times administration of contrast medium in 10 patients was not followed by the development of renal dysfunction. None of the present cases who were submitted to intravenous pyelography (IVP), five times in total, developed renal dysfunction, suggesting that IVP may not be a trigger for renal dysfunction. Notwithstanding, since this problem is not yet resolved, we are of the opinion that the use of IVP in MM patients should be avoided, as pointed out by Rota et al (13). Comparison of serum creatinine levels before and after the use of contrast medium was possible in 13 cases. Three (75%) of the four cases who had serum creatinine $\geq 133 \mu\text{mol/L}$ (1.5 mg/dL) before the use of contrast medium subsequently required dialysis. The effect of dehydration, which is known to enhance the risk of renal dysfunction due to contrast medium (3, 18), was not evaluated in many of the present cases. The present results indicate that the use of contrast medium in MM patients with already compromised renal function may further decrease their remaining function.

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