Monoclonal Proteinuria as a Prognostic Factor for Multiple Myeloma Patients with Intact Immunoglobulin Type

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Background: Urine/serum protein electrophoresis (PEP) and immunofixation electrophoresis (IEP) for monoclonal protein (M-protein) are used for initial evaluation in patients with multiple myeloma. We evaluated the prognostic significance of M-proteinuria status and its association with other prognostic factors.

Methods: Between December 2002 and December 2004, 64 de novo symptomatic multiple myeloma patients with intact immunoglobulin (Ig) type were divided into two groups according to their initial urine PEP/IEP findings.

Results: Twenty-seven patients with undetectable or free light-chains only were classified into F group, and 37 with whole Ig with or without light-chains were classified into W group. The two groups were similar in sex, age, performance, azotemia, β2-microglobulin, stage and treatment, but M-protein concentration was significantly higher in the W than in F group (5.1 vs 1.3g/dL, $P<0.01$). The overall response rate was significantly higher in F group than in W group (80.8% vs 63.6%, P=0.02), whereas the 2-year OS rate did not differ significantly between the groups (81.0% vs 57.7%, P=0.15).

Conclusion: Monoclonal proteinuria is helpful in identifying patients with advanced disease and poorer prognosis in multiple myeloma. ***(Korean J Hematol 2007;42:276-282.)***

Key Words: Multiple myeloma, Proteinuria, Prognosis

INTRODUCTION

Urine and serum protein electrophoresis (PEP) and immunofixation electrophoresis (IEP) are routinely used in the initial diagnosis and evaluation of patients with multiple myeloma, with detection of monoclonal protein (M-protein) in serum or urine considered diagnostic of multiple myeloma. In patients with intact Immunoglobulin (Ig) type multiple myeloma, however, the urinary electrophoresis findings are usually ignored, due to the convenience of disease monitoring with serum M-protein.

Renal failure is a common complication in myeloma patients. Its pathogenesis is multifactorial and may include hypercalcemia, myeloma cast nephropathy due to urinary excretion of light-chains, dehydration, infection, and the effects of non-steroidal anti-inflammatory agents and radiological contrast media. Renal failure is considered a marker of greater tumor

접수 : 2007년 7월 13일, 수정 : 2007년 8월 7일
승인 : 2007년 8월 10일
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burden, as well as being related to disease progression.[1] Serum parameters, however, are less sensitive in detecting renal damage caused by excretion of light-chains,[2] moreover, abnormal levels of these parameters are indicative of disease with more advanced stage.

Plasma cells synthesize and secrete only a single recombined Ig and a minor excess of the corresponding κ or λ light-chain.[3] Whereas intact or whole Ig molecules are larger and do not cross the intact glomerular basement membrane, free κ and λ light-chains, which are low-molecular weight proteins, therefore enter the glomerular filtrate. Myeloma kidney and light-chain proteinuria result from the excessive excretion of light chains, with progressive tubulointerstitial and glomerular damage leading to the secretion of whole Ig molecules into the urine.[1,3]

To our knowledge, the clinical significance of the M-proteinuria status in myeloma patients has never been evaluated, and it is unclear whether more advanced renal damage is observed in patients with urinary whole Ig molecules than in those with light-chain proteinuria only. We therefore evaluated the characteristics of patients according to M-proteinuria status and we assessed the clinical significance of M-proteinuria status at the time of diagnosis of symptomatic multiple myeloma.

MATERIALS AND METHODS

1. Patients

We retrospectively reviewed the medical records of patients newly diagnosed with multiple myeloma at Asan Medical Center between December 2002 and December 2004. Eligibility criteria included only symptomatic multiple myeloma with no coexisting malignancy, no history of previous chemotherapy and performance status of 0～3 according to the Eastern Cooperative Oncology Group scale. Diagnosis was based on the criteria of the International Myeloma Working Group.[4] Patients were divided into two groups according to their urine electrophoresis results at the time of multiple myeloma diagnosis. Patients with undetectable urinary M-proteins or free light-chains only were classified into the free light-chain (F) group, whereas patients with urinary whole Ig, with or without light- chains, were classified into the whole Ig (W) group.

2. Methods

M-proteins in serum and urine were detected and identified by protein and immunofixation electrophoresis with a commercial kit (Beckman Coulter PARAGON system, California, USA). Azotemia was defined as a serum creatinine concentration $\geq$1.4mg/dL by the department of laboratory medicine in our center. Initial treatment consisted of VAD (vincristine 0.4mg and doxorubicin 9mg/m^2 by continuous intravenous (IV) infusion over 24 hours for 4 days with dexamethasone 40mg/ day per os (PO) on days 1～4, 9～12, and 17～20 every 4 weeks) for candidates for autologous stem cell transplantation (ASCT), or thalidomide (200mg/day on days 1～14 every 4 weeks) for elderly or poor performance patients. Supportive care for pain control consisted of pamidronate (90mg IV over 2 hr every 4 weeks) or zolendronate (4mg IV over 15 min every 4 weeks), and critical bone lesions were treated with radiotherapy. Because the retrospective studies do not have responsibility of approval in the institutional review board (IRB) of our center, we did not submit our study protocol to IRB. However all patients provided written informed consent, and the IRB approved the treatment of all patients, especially ASCT protocol of myeloma.

3. End point and statistical consideration

The primary endpoint was overall survival (OS). The secondary endpoints were overall response to initial treatment and relationship to initial M-proteinuria status and other prognostic factors. OS was calculated from the time of diagnosis to death from any cause. Response to treatment was assessed according to the new EBMT/ IBMTR/ABMTR criteria.[5] The basic characteristics of two groups were compared by using t-test or the χ^2 test, where appropriate. Survival curves were estimated using the Kaplan-Meier method. To assess the relative significance of potential prognostic factors, we performed univariate and mul-

tivariate analyses using the Log-Rank test and the Cox proportional hazards models, respectively. A P value < 0.05 was considered statistically significant, and all analyses were performed using SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Patient characteristics

Between December 2002 and December 2004, a total of 96 patients were newly diagnosed with plasma cell disorders at Asan Medical Center; of these, 64 were diagnosed with symptomatic multiple myeloma. Baseline characteristics of patients in two groups are shown in Tables 1 and 2. Median age, sex distribution and performance status were comparable between two groups. In W group, more patients had advanced anemia, hypoalbuminemia, high levels of M-protein, elevated lactate dehydrogenase (LDH) and more plasma cells in the bone marrow (BM). Although not statistically significant, W group consisted of patients with more advanced International Staging System (ISS) stage[6] and higher levels of C-reactive protein (CRP).

2. Treatment and outcomes

Initial treatment was given to 26 patients (96.3%) in F group, and 31 (83.8%) in W group. VAD regimen administered to 18 patients in F group and 24

Table 1. Patient demographic and clinical characteristics at baseline

	F group n (%)	W group n (%)	*P* value
No. of patients	27 (100.0%)	37 (100.0%)	
No. of males	17 (63.0%)	17 (45.9%)	0.13
Median age (range)	59 yrs (42~77)	61 yrs (41~82)	0.45
Median f/u time (range)	24.9 months (14.1~37.4)		
ECOG (PS) 1	21 (77.8%)	25 (67.6%)	0.54
2	4 (14.8%)	6 (16.2%)	
3	2 (7.4%)	6 (16.2%)	
ISS stage I	4 (14.8%)	1 (2.7%)	0.09
II	14 (51.9%)	16 (43.2%)	
III	9 (33.3%)	20 (54.1%)	

Abbreviations: PS, performance status; ISS, International staging system.

Table 2. Patient laboratory characteristics at baseline

	F group median (range)	W group median (range)	*P* value
M-protein (g/dL)	1.3 (0.1~6.2)	5.1 (0.9~10.5)	***0.001***
BJ protein (mg/24 hr)	53.2 (0~6,980)	385.1 (9~6,044)	0.78
Hb (g/dL)	10.5 (6.3~14.0)	8.4 (4.7~13.8)	***0.008***
Albumin (g/dL)	3.1 (2.0~4,1)	2.6 (1.3~3.8)	***0.001***
Calcium (mg/dL)	9.3 (7.9~14.1)	9.3 (7.8~14.5)	0.84
CRP (mg/dL)	0.50 (0.07~10.86)	0.85 (0.03~19.85)	0.13
Creatinine (mg/dL)	1.0 (0.4~10.9)	1.2 (0.5~5.5)	0.53
Azotemia patients (n, %)	9 (33.3%)	10 (27.0%)	0.59
B2-MG (ug/mL)	4.4 (0.8~29.8)	6.1 (2.1~21.8)	0.80
LDH (IU/L)	195.0 (100~771)	163.0 (79.0~437.0)	***0.04***
Plasma cell in BM	30.8% (6.2~96.2)	53.1% (1.2~97.2)	***0.03***

Abbreviations; BJ protein, Bence-Jones protein; CRP, C-reactive protein; B2-MG, β_2-microglobulin; LDH, lactate dehydrogenase; BM, bone marrow.

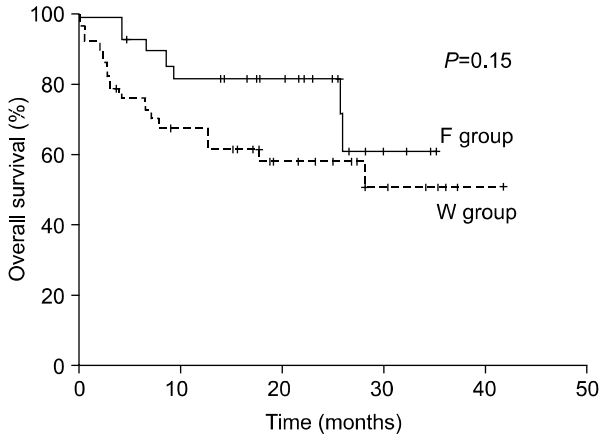

Fig. 1. Overall survival curves relative to M-proteinuria.

patients in W group, whereas thalidomide to 8 patients in F group, and 7 patients in W group. ASCT was performed in 23 patients (12 patients in F group, 11 patients in W group). The overall response (complete and partial response) rate to initial treatment was 80.8% in F group (95% CI, 65.7～95.9%) and 63.6% in W group (95% CI, 50.1~83.3%), respectively (P=0.02).

3. Survival outcome

At the time of analysis, 31 patients, 17 in F group and 14 in W group, were alive. The 2-year OS rates were 81.0% in F group (95% CI, 66.2～95.8%) and 57.7% in W group (95% CI, 41.8～73.6%) (P=0.15, Fig. 1).

4. Prognostic factors affecting survival

Univariate analysis showed that performance status (PS) and CRP level were significantly associated with OS. In multivariate analysis, it also showed that PS and CRP level were the independent prognostic factor affecting OS (Table 3).

DISCUSSION

We have investigated the clinical significance of M-proteinuria in patients with multiple myeloma. Although serum β_2-microglobulin and albumin levels are considered the most important prognostic factors for survival, many other prognostic factors have been identified, including anemia, serum calcium, serum creatinine, severity of bone lesions, level and type of M-protein, CRP, serum albumin, del (13) and labeling index for proliferative activity.[6,7]

Renal impairment occurs in 50% of patients during the course of multiple myeloma, and 20～30% of patients present with some degree of renal dysfunction at diagnosis.[8,9] Renal failure often seems to be a manifestation of high tumor burden. Only renal biopsy can define exactly the type and degree of renal damage, which will play an important diagnostic and prognostic role.[10] However, it cannot be performed in the routine approach because of its potential related risk. Since reversibility of renal failure is related to its severity, early identification of renal damage followed by a prompt and effective therapy increases the possibility to obtain normalization of the renal function.[11-13]

Although renal damage in this disease is due to many factors, and one component cannot explain the entire process of renal failure, the urinary excretion of high amounts of light-chain protein may cause proximal tubular damage, making patients more susceptible to this complication. Extensive bone destruction also promotes renal failure by hypercalcemia. Although many patients show renal impairment at diagnosis, about half of these may recover renal function, usually within the first 3 months.[14,15] To prevent and/or reverse renal failure, it is important to identify the border of reversible and irreversible renal damage.

Some authors reported on the role of urinary proteins (α1-microglobulin, β2-microglobulin, albumin and IgG) to define the function of proximal tubule or glomerular filtration and the role of 24 hr-urinary creatinine clearance to indices advanced myeloma.[2,16-18] Although no clinical study has evaluated the sequential process of renal damage, whole Ig proteinuria is suggested to reflect the later stages of cast nephropathy.[3] Therefore, patients with whole Ig proteinuria are thought to be predisposed to renal impairment and to require promptly effective treatment.

Although our study showed the significant difference in response rate, it was failed to show that M-proteinuria status was significantly prognostic of

Table 3. Univariate and multivariate analysis of clinicopathologic factors associated with overall survival

Factors (n)	2-year OS	Univariate *P* value	Multivariate	
			P value	Hazard ratio
Age				
>60 years (31)	57.7%	0.14	0.34	1.55 (0.63~3.82)
≤60 years (33)	77.0%			
Gender				
Male (34)	66.8%	0.56	0.78	1.14 (0.46~2.83)
Female (30)	68.4%			
ECOG (PS)				
2/3 (18)	27.5%	*<0.01*	*<0.01*	4.17 (1.68~10.39)
0/1 (46)	80.1%			
ISS stage				
Stage III (29)	62.4%	0.25	–	–
Stage I, II (35)	71.4%			
Urine electrophoresis				
Whole Ig (37)	57.7%	0.15	0.13	2.12 (0.79~5.67)
FLC/undetectable (27)	81.0%			
M-protein				
>3.7g/dL (32)	66.9%	0.74	–	–
≤3.7g/dL (32)	68.2%			
Hb				
<8.0g/dL (22)	63.7%	0.59	–	–
≥8.0g/dL (42)	75.0%			
Albumin				
<3.3g/dL (51)	60.9%	0.08	–	–
≥3.3g/dL (13)	92.3%			
Calcium				
>10.0mg/dL (16)	55.6%	0.08	–	–
≤10.0mg/dL (48)	71.9%			
C-reactive protein				
>0.5mg/dL (33)	57.1%	*0.02*	*0.03*	3.02 (1.14~7.99)
≤0.5mg/dL (31)	82.1%			
Creatinine				
≥1.4mg/dL (22)	54.8%	0.06	–	–
<1.4mg/dL (42)	73.3%			
β_2-microglobulin				
>2.4ug/dL (58)	65.8%	0.67	–	–
≤2.4ug/dL (6)	83.3%			
LDH				
>250IU/L (18)	56.3%	0.28	–	
≤250IU/L (46)	75.0%			
Plasma cells in BM				
>33% (38)	66.8%	0.86	–	–
≤33% (24)	70.2%			

Abbreviations: FLC, free light-chain; See Table 1, 2.

overall survival. Neither whole Ig proteinuria nor other prognostic factors, such as stage, age, LDH, anemia and β2-microglobulin, was also statistically significant in univariate analysis. The failure to show the significant differences in OS rate is implied due to the different numbers of patients with ASCT in two

groups. Since our study had several limitations, including its retrospective design, the small number and heterogeneity of patients and treatments, additional prospective clinical studies are required to determine the clinical significance of monoclonal proteinuria status and its relationship with other prognostic factors.

In conclusion, this is, to our knowledge, the first clinical attempt to define the role of M-proteinuria status in patients with symptomatic multiple myeloma. Although the M-proteinuria status could not correlate with survival outcome, it seems to be helpful in identifying a subset of patients with advanced disease and poorer prognosis.

요 약

배경: 소변에서의 단백 전기영동과 면역고정 전기영동은 다발골수종 환자의 초기 평가에서 단클론 단백여부를 알아보기 위해 사용된다. 단클론 단백뇨 상태의 예후 인자로서의 중요성에 대해 평가하였다.

방법: 2002년 12월부터 2004년 12월까지 완전 면역글로불린형의 다발골수종을 처음 진단받은 환자 64명을 대상으로 처음 소변의 단클론 단백뇨 상태에 따라 두 군으로 나누고 생존율과 다른 예후인자들과의 관계를 분석하였다.

결과: 단클론 단백뇨가 검출되지 않거나 유리경쇄만 검출된 환자군(27명, F군)과 전면역글로불린형의 환자군(37명, W군)으로 나누었다. 두 군사이의 성별, 나이, 활동도, 질소혈증, 베타2-마이크로글로불린, 병기 및 치료에서는 차이가 없었고, 단클론 단백의 농도가 W군에서 유의하게 높았다(5.1 vs 1.3g/dL, $P<0.01$). 치료에 대한 전체 반응률은 F군에서 유의하게 높았고(80.8% vs 63.6%, $P=0.02$), 2년 생존율은 두 군 간에 유의한 차이를 보이지 못했다(81.0% vs 57.7%, $P=0.15$).

결론: 단클론 단백뇨는 다발골수종 환자의 진행 상태와 불량한 예후를 예측하는데 도움이 될 수 있다.

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