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Renal impairment in patients with multiple myeloma

多發性骨髓瘤患者的腎損害

Objectives. To determine the incidence of multiple myeloma in the Eastern District of Hong Kong Island, the degree of renal impairment at presentation, and its relationship with haematological and biochemical parameters and survival.
Design. Retrospective study.
Subjects and methods. Patients with myeloma who were admitted to a regional hospital in Hong Kong from January 1994 to March 2000 were included. Demographic data, type and stage of multiple myeloma, degree of renal impairment, haematological and biochemical parameters, and survival data were analysed.
Results. There were 64 patients (28 male, 36 female) in the study. The incidence rate for multiple myeloma in this group was 1.78 per 100 000 population. Immunoglobulin G (53.1%) was the most common type of multiple myeloma seen, followed by immunoglobulin A (29.7%), light-chain (12.5%), and immunoglobulin D (4.7%). Nineteen (29.7%) patients had serum creatinine levels of greater than 177 μmol/L at presentation. Renal impairment was more common in patients with light-chain multiple myeloma (P=0.081). The serum creatinine level was not significantly correlated with haemoglobin level (r= –0.21), platelet count (r=0.04), serum calcium level (r=0.08), or albumin level (r= –0.03). The median survival time for patients with multiple myeloma was 592 days (95% confidence interval, 229-955). Serum creatinine level at presentation was significantly associated with survival (P=0.017). Patients with a creatinine level of less than 400 μmol/L had longer survival (P=0.042). Infection was the most common cause of death (32.8%).
Conclusion. The incidence rate noted was comparable to other published studies. Renal impairment at presentation was common in patients with multiple myeloma and was associated with poor survival.

目的：研究香港島東區多發性骨髓瘤的發病率，及患者求診時的腎損害程度；並研究其與血液學參數、生化學參數和存活率的關係。
設計：回顧性研究。
對象與方法：就1994年1月至2000年3月香港一所地區醫院內的多發性骨髓瘤患者，分析其人口統計學數據、多發性骨髓瘤的類型和病期、腎損害程度、血液學及生化學參數、以及存活數據。
結果：本研究包括64名患者(28男， 36女)。研究地區的多發性骨髓瘤發病率為每10萬人口1.78人。免疫球蛋白G是最常見的多發性骨髓瘤類型(53.1%)，其次為免疫球蛋白A (29.7%)、輕鏈(12.5%)以及免疫球蛋白D (4.7%)。19名(29.7%)患者求診時的血清肌酸酐水平超過177 μmol/L。腎損害在輕鏈型多發性骨髓瘤患者中較為常見(P=0.081)。血清肌酸酐水平與血色素水平(r=–0.21)、血小板數(r=0.04)、血清鈣水平(r=0.08)或血蛋白水平(r=–0.03)，均無重要關係。患者的中值存活期是592天(95%置信區間，229-955)。血清肌酸酐水平與存活率有重要關係(P=0.017)。肌酸酐水平低於400 μmol/L的患者存活期較長(P=0.042)。感染是最常見的死亡原因(32.8%)。
結論：研究地區的多發性骨髓瘤發病率與其他已發表的研究結果相近。多發性骨髓瘤患者經常呈現腎損害，而且存活率並不理想。

Key words:
Dialysis;
Kidney failure;
Multiple myeloma;
Survival

關鍵詞：
透析；
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Introduction

Multiple myeloma is the result of malignant clonal formation of plasma cells. It is largely a disease of elderly people, with a median age of onset of 70 years.[1,2] Renal impairment is relatively common and up to 22.2% of patients have a

serum creatinine level of greater than 177 μmol/L (reference range, 53-106 μmol/L) at diagnosis.[3] Renal impairment in patients with multiple myeloma may be secondary to dehydration, hypercalcaemia, myeloma of the kidney, or light-chain and heavy-chain deposition disease. The degree of renal failure is usually moderate, and reversible in approximately 50% of patients, especially when related to precipitating factors such as hypercalcaemia, or fluid depletion.[4,5] The proportion of patients with severe renal failure at presentation has been reported to range from 1.8% in unselected patient groups to 12.7% in selected populations.[4,5]

The purpose of this study was to determine the incidence of multiple myeloma in the population residing in the Eastern District of Hong Kong Island, along with the degree of renal impairment at presentation, its relation to haematological and biochemical parameters, and the overall survival of this patient group.

Subjects and methods

Subjects

All patients with multiple myeloma admitted to the Pamela Youde Nethersole Eastern Hospital between January 1994 and March 2000 were recruited. Multiple myeloma was diagnosed if any two of the following criteria were evident: plasma cells infiltrate of the bone marrow of greater than 15%, presence of serum or urinary monoclonal paraprotein, and radiographic evidence of osteolytic skeletal lesions. Demographic information and clinical data, including type of multiple myeloma, cell count, renal function, renal biopsy results, and survival data, were collected.

Statistical analysis

Data were expressed as mean values with standard deviation (SD). Pearson's correlation analysis was used to evaluate the relationship between serum creatinine level and haematological parameters, serum calcium, and serum albumin levels. Multiple logistic regression models were used to detect if there was a relationship between haematological parameters, serum calcium level, serum albumin level, or serum creatinine level and survival. The Kaplan-Meier method was employed for the survival analysis.

Results

There were 64 patients in the study group. Patients' demographic and clinical characteristics are reported in Table 1. The population of Eastern District in Hong Kong Island is approximately 600 000, giving an annual incidence rate of 1.78 per 100 000 population. Immunoglobulin G (IgG) myeloma was the most common type seen, followed by immunoglobulin A (IgA), light-chain, and immunoglobulin D (IgD) myeloma. Fifty-three (82.8%) patients had stage III disease.

The mean serum creatinine level of the study group was 258 μmol/L (SD, 332 μmol/L). Serum creatinine levels in relation to the type of myeloma are shown in Table 2. Using a serum creatinine level of 177 mmol/L as the cut-off point for renal impairment, light-chain myeloma was more frequently associated with renal impairment, although this association was not statistically significant (P=0.081). The serum creatinine levels in relation to different disease stages were as follows: stage I, 81 μmol/L (SD, 18 μmol/L); stage II, 185 μmol/L (SD, 140 μmol/L); and stage III, 279 μmol/L (SD, 358 μmol/L). Pearson correlation analysis indicated that the level of serum creatinine was not significantly correlated with haemoglobin level (r= –0.21), platelet count (r=0.04), serum albumin level (r= –0.03), or corrected calcium level (r=0.08).

Table 1. Demographic data and clinical characteristics for patients with multiple myeloma (n=64)

Data/characteristics	No. of patients
Male/female	28/36
Age (SD) [years]	66.8 (12.3)
Type of myeloma	
Immunoglobulin G	34 (53.1%)
Immunoglobulin A	19 (29.7%)
Immunoglobulin D	3 (4.7%)
Light-chain	8 (12.5%)
Stage of myeloma[6]	
I	3 (4.7%)
II	8 (12.5%)
III	53 (82.8%)

The characteristics of patients requiring plasmapheresis and/or dialysis are outlined in Table 3. Plasmapheresis was recommended for patients with acute renal failure due to paraprotein load, while chemotherapy took effect. Seven patients underwent plasmapheresis for a mean of 4 sessions (range, 1-5 sessions). Patient 8 was unable to tolerate plasmapheresis because of unstable haemodynamic parameters. Patient 9 declined plasmapheresis but subsequently agreed to dialysis when complications of uraemia arose. The median survival time of patients receiving plasmapheresis was 459 days (95% confidence interval [CI], 0-1257). Dialysis was scheduled if there were uraemic symptoms, electrolyte disturbances, or fluid retention. Six patients required acute dialysis support in the form of haemodialysis or haemodiafiltration. Treatment for three of these patients was later changed to peritoneal dialysis—one to intermittent peritoneal dialysis, and two to continuous ambulatory peritoneal dialysis (CAPD). Five (83.3%) of the six patients died during the study period. The median survival time for patients requiring acute dialysis was 76 days. The surviving patient was treated with CAPD at the end of the study.

Percutaneous renal biopsy was performed in eight patients with irreversible renal impairment or nephrotic syndrome. Six patients were found to have myeloma cast nephropathy, one had light-chain (AL) amyloidosis (primary amyloidosis), and one had normal findings. Four of the six patients with cast nephropathy required plasmapheresis, with two also requiring dialytic support. The remaining two patients with cast nephropathy had chronic renal failure despite chemotherapy. The patient with amyloidosis received plasmapheresis and dialysis. The patient with a normal renal biopsy result had the biopsy 9 months

Table 2. Serum creatinine levels with respect to multiple myeloma type

Type of myeloma	No. of patients	Mean serum creatinine (SD) [μmol/L]	Range (μmol/L)
Immunoglobulin G	34	259.6 (351.6)	60-1818
Immunoglobulin A	19	206.8 (282.3)	65-999
Immunoglobulin D	3	429.7 (527.8)	117-1039
Light-chain	8	308.9 (323.3)	63-1032
Total	64	258.0 (332.4)	60-1818

Table 3. Characteristics of patients requiring plasmapheresis and/or dialysis

Patient	Sex	Age (years)	Type of myeloma	Stage of myeloma	Biopsy result	No. of plasmapheresis sessions	Dialysis (mode)	Survival (days)
1	F	81	IgG*	III	ND‡	5	ND	536
2	M	48	Light-chain	III	Cast nephropathy	5	ND	459
3	M	27	Light-chain	III	Cast nephropathy	2	ND	1026††
4	M	76	IgG	III	ND	1	HDF§	22
5	M	62	Light-chain	III	Amyloidosis	5	HD‖ IPD¶	148
6	M	48	IgG	II	Cast nephropathy	5	HD CAPD**	602††
7	M	68	IgD†	III	Cast nephropathy	5	HD	76
8	M	77	IgG	III	ND	ND	HDF	60
9	F	61	IgG	III	ND	ND	HD CAPD	553

* IgG immunoglobulin G
† IgD immunoglobulin D
‡ ND not done
§ HDF haemodiafiltration
‖ HD haemodialysis
¶ IPD intermittent peritoneal dialysis
** CAPD continuous ambulatory peritoneal dialysis
†† These are censored data (ie death has not been reached by the patients at the end of this study)

after the diagnosis of IgG myeloma to investigate nephrotic syndrome.

The median survival time was 592 days (95% CI, 229-955). Twenty-one (61.8%) patients with IgG myeloma survived. The median survival time for patients with IgA, IgD, and light-chain myeloma were 496 days (95% CI, 205-787), 235 days (95% CI, 0-489), and 459 days (95% CI, 143-775), respectively. Patients with IgD myeloma had the worst prognosis on Kaplan-Meier analysis, although this did not reach statistical significance (log-rank test, P=0.083). Using Cox regression analysis, serum creatinine level was shown to be associated with patient survival (P=0.017), while haemoglobin level (P=0.318), platelet count (P=0.783), serum albumin level (P=0.063), and corrected calcium level (P=0.358) were not associated.

Kaplan-Meier analysis showed that patients with a serum creatinine level of less than 400 μmol/L at presentation had significantly better survival (Fig). The median survival time of patients with a serum creatinine level of less than 400 μmol/L was 881 days (95% CI, 29-1733), while those with a serum creatinine level of greater than 400 μmol/L had a median survival time of 148 days (95% CI, 0-640). In total, 36 (56.3%) of the 64 patients died during the study period. The causes of death were infection (32.8%), relapse of myeloma (6.3%), cerebrovascular accident (4.7%), withdrawal of dialysis (4.7%), cardiac disease (1.6%), and hepatic failure (1.6%).

Discussion

The annual incidence of multiple myeloma in the Eastern District of Hong Kong Island determined by this study is comparable to the quoted annual incidence rates in western populations of 2 to 4 per 100 000 population.[7,8] These studies have also similarly reported that IgG myeloma was the most common type of myeloma seen.

Of the different biochemical parameters and clinical features recorded at presentation in this study, only renal impairment was found to be significantly associated with survival (P=0.017). The literature indicates that as many as 50% of patients with multiple myeloma may experience some degree of renal insufficiency, although in the majority, renal function will improve in response to simple measures, such as rehydration, correction of hypercalcaemia, or

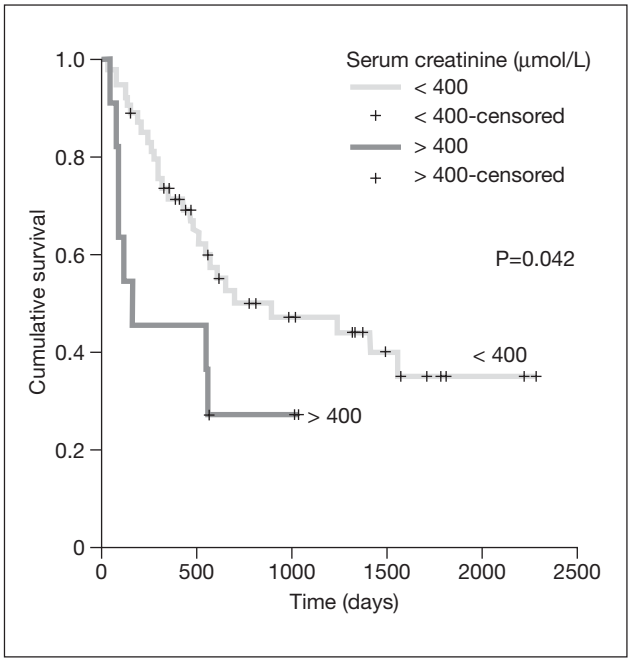

Fig. Survival of patients with multiple myeloma according to serum creatinine level at presentation

discontinuation of nephrotoxic drugs.[4,9-12] In this study, 29.7% of patients had creatinine levels of greater than 177 μmol/L at presentation, and the proportion of patients with multiple myeloma and renal failure requiring dialysis was 9.3%. Torra et al[5] found the proportion of patients requiring dialysis in their case series was somewhat higher at 12.7%. This discrepancy could reflect referral bias for dialysis, with a higher proportion of elderly patients and patients with an advanced disease state in this study.

Most patients with multiple myeloma who do not regain normal renal function will have residual mild-to-moderate renal impairment. Patients with renal impairment requiring acute dialysis support are treated with haemodialysis and haemodiafiltration. The use of citrate as an anticoagulant not only achieves regional anticoagulation, limiting the risk of bleeding in thrombocytopenic patients but, as citrate can chelate calcium, also treats hypercalcaemia.[13] Sharland et al[14] evaluated mortality in 140 patients with multiple myeloma and found that the median survival time was 22 months both for patients with renal failure treated with dialysis and those with lesser degrees of renal dysfunction. This finding suggests that dialysis may provide a significant survival benefit for patients with end-stage renal failure. Progression to end-stage renal disease can be treated with haemodialysis or peritoneal dialysis.[5,15] Although no survival difference between patients managed with peritoneal dialysis or haemodialysis has been reported, patients undergoing peritoneal dialysis have been noted to have a significantly higher prevalence of infection, largely peritonitis.[2,15] Infection in the form of CAPD peritonitis or gram-positive septicaemia in patients undergoing haemodialysis has been shown by Korzets et al[15] to be a common complication of renal replacement therapy. Peritonitis rates reported range from one episode per 5.6 patient-months to one episode per 14.4 patient-months.[15,16] Six patients in this study received acute dialysis support, three subsequently changing to long-term peritoneal dialysis—one to intermittent peritoneal dialysis and two to CAPD. One of the two patients receiving CAPD had three episodes of *Pseudomonas aeruginosa* exit-site infection. The other had one episode of exit-site infection and one episode of culture-negative peritonitis.

Seven patients in this study received plasmapheresis. Plasmapheresis and chemotherapy have been reported to lower the serum myeloma protein level much more rapidly than chemotherapy alone.[17] Moist et al[18] reviewed a group of 24 patients with multiple myeloma, all of whom received hydration, standard chemotherapy, and plasmapheresis. They suggested that plasmapheresis may prevent the initiation or continuation of dialysis in patients with rapidly progressive renal failure secondary to multiple myeloma.

Previous series of patients with multiple myeloma have shown median survival periods ranging from 240 to 660 days.[2,5,17,19,20] In the current group, the median survival time was 592 days (95% CI, 229-955). This is attributed to differences in the selection of patients, requirement for dialysis support, and chemotherapy regimens. Patients with a serum creatinine level of less than 400 μmol/L at presentation had a significantly longer survival (P=0.042). This is in keeping with other studies showing that renal impairment at the time of diagnosis is associated with poorer survival.[9,21,22] Alexanian et al[4] have suggested that myeloma mass is more important than the presence or degree of azotaemia in adversely affecting prognosis, however.

Of the six patients who required acute dialysis support, five died during the study period. The median survival time of patients requiring acute dialysis support was 76 days. Two of the patients were receiving long-term renal replacement therapy in the form of CAPD. One survived to the end of the study (more than 602 days), the other died 553 days after the diagnosis of multiple myeloma. The disparity between the median survival time of these patients receiving dialysis and those of Sharland et al's[14] group suggests that factors other than dialytic support contributed to the survival of patients with renal failure. These factors may include the tumour load and response to chemotherapy.

Percutaneous renal biopsy was performed for eight patients in the study group. Six patients were found to have cast nephropathy, one amyloidosis, and one patient had normal findings. In the study by Montseny et al,[23] histological findings for 118 renal biopsies were as follows: 40.7% myeloma cast nephropathy, 10.2% tubulo-interstitial nephritis, 29.7% amyloidosis, and 18.6% light-chain deposit disease (LCDD).[23] Montseny et al[23] found that the median survival time was 1 year with cast nephropathy, 2 years with AL-amyloidosis, and 4 years for patients with LCDD. These data highlight the usefulness of renal biopsy, both as a diagnostic and a prognostic procedure.

Torra et al[5] found infection to be the most common cause of death for patients with multiple myeloma, as did the current study. Irish et al[2] similarly showed that more than half of their patients had at least one significant infectious event and that 25% of deaths were related to infection, particularly pulmonary or intra-abdominal infection.[2] Montseny et al's[23] study followed 118 patients in five nephrology units between 1975 and 1994. Sixty-one patients died, with the most common causes of death being cardiac disease, infection, and withdrawal of dialysis and haemorrhage.

Conclusion

The incidence of multiple myeloma in the Eastern District of Hong Kong Island was found to be comparable with other published incidence rates. The presence of renal impairment in patients with multiple myeloma at presentation was common and, as with other studies, was shown to have a significant impact on survival. The most common cause of death was infection, followed by relapse of myeloma.

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