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Presentation and survival of patients with severe renal failure and myeloma

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Summary

We reviewed the clinical features and outcome of 56 patients with myeloma and severe renal failure managed in a single institution over a 15-year period. Renal failure was recognized within 2 months of the diagnosis of myeloma in 75% of patients, and was the initial presentation of myeloma in 50%. Patients were staged by the Durie and Salmon classification. Light-chain and IgD myeloma accounted for 46% of cases, and Bence-Jones proteinuria was identified in >90%. In 43%, a potential precipitant of renal failure was identified, usually hypercalcaemia or a non-steroidal anti-inflammatory agent. A preserved corrected calcium at presentation was characteristic (2.40 ± 0.15 mmol/l, $n=42$), even after excluding those with hypercalcaemia requiring specific intervention ($n=14$, 2.76 ± 0.51; $p<0.01$): this finding in patients with unexplained acute renal failure should alert clinicians to the possibility of myeloma. Forty-seven patients (84%) required dialysis. Only seven (15%) ever regained renal function. Median survival (all patients) was 8 months. One-third died within 3 months of referral and one-third survived >1 year. Hypoalbuminaemia and reduced platelet count at presentation were associated with reduced survival, but hypercalcaemia, infection, dialysis (urgent or long-term), and dialysis modality were not. Chemotherapy was associated with increased survival, but progression of myeloma and infection were the two most frequent causes of death. Severe renal failure was associated with advanced myeloma stage and light-chain/IgD paraproteinaemia. Survival was related to severity of myeloma and not requirement for dialysis *per se*.

Introduction

The annual incidence of myeloma is 20–40 per million population, but it is largely a disease of the elderly with a median age at presentation of ~70 years.[1,2] Although chemotherapy has improved survival over the last 20 years, myeloma remains an incurable disease. The median survival is approximately 36 months in unselected populations, but ranges from 14 months in those with stage III disease to 60 months in stage I.[3] At presentation, 20% of patients have renal impairment of some degree and during the course of the disease renal failure affects up to 50% of patients.[4] In the majority, renal failure improves in response to rehydration, control of hypercalcaemia and following initiation of chemotherapy. Renal failure has been recognized as an adverse feature affecting survival since the introduction of the staging system of Durie and Salmon,[5] and later confirmed in prospective and retrospective studies.[6,7] Renal damage appears more likely in those with light chain and IgD myeloma[8,9] and particularly with the presence of urinary light chains (Bence-Jones proteinuria), although the toxicity of light chains is highly variable for reasons that are incompletely understood (reviewed in reference 10). The proportion of patients with severe renal failure at presentation ranges from 2% in unselected to 12% in selected populations.[4,11,12] The avoidance of the need for maintenance dialysis by recovery of renal

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function in myeloma patients with severe acute renal failure has been reported to improve survival,[13,14] but other studies suggest that the need for dialysis *per se* does not impair survival.[12,15] To identify the clinical features of patients with severe renal failure and myeloma, their characteristics at presentation and the factors influencing survival, we reviewed the experience at our institution over a 15-year period.

Methods

We reviewed the records of all patients referred to the Oxford Renal Unit with a possible diagnosis of myeloma from 1980 to the end of 1994 (15 years). Of 66 patients identified, nine were referred in the 8-year period 1980–1987 and 57 in the 7-year period 1988–1994. All patients had a paraprotein, but in 10 other pathological diagnoses including primary amyloidosis ($n=1$), fibrillary glomerulonephritis ($n=1$), mesangiocapillary glomerulonephritis ($n=1$), and chronic renal failure of other cause ($n=2$) or insufficient evidence to confirm a diagnosis of myeloma ($n=5$) led to their exclusion. We analysed the outcome of the remaining 56 patients by reference to hospital records and follow-up from their referring physicians, hospitals and general practitioners. Only six patients (11%) were alive at the time of censure (1/7/95); 265, 436, 578, 601, 1320 and 1418 days after referral to the renal unit.

A diagnosis of myeloma was made if the patient fulfilled any two of the following criteria: a neoplastic plasma cell infiltrate of the bone marrow; radiographic evidence of osteolytic skeletal deposits; a serum or urinary monoclonal paraprotein. The disease was staged according to Durie and Salmon.[5] Before 1989, serum paraprotein levels were not routinely quantified, and measurements were available in only 40 patients. Urinary paraprotein was not routinely quantified until 1993, and is therefore recorded as detected or not detected. Fifty-one patients had undergone complete or limited skeletal radiographic surveys, 51 had had a bone-marrow examination, and 22 patients had undergone renal biopsy. All patients had renal ultrasound examination and/or additional imaging to exclude other causes of renal failure. All biochemical and haematological data shown is that obtained on admission to the Oxford Renal Unit. Results for patients who were treated for hypercalcaemia or were transfused prior to transfer reflect these treatments. A categorical classification of hypercalcaemia was made if the presenting calcium, corrected for albumin, was >2.90 mmol/l and did not respond to rehydration alone, and included patients whose treatment for hypercalcaemia was initiated at the referring hospital.

Statistics

Comparison of means or medians is by ANOVA or Kruskall-Wallis ANOVA, respectively. χ^2 analysis was used to compare categories and groupings. Survival time was log-transformed for stepwise regression study. The survival curve was derived by the Kaplan-Meier technique. Data was analysed by Statview II (Abacus Concepts, California) and Prism (Graph Pad Software, USA) computer software programs.

Results

The personal, metabolic, diagnostic and treatment data of the 56 patients are shown in Table 1, and the classification of myeloma according to the paraprotein type is summarized in Table 2. The median age of the patients was 67, with a slight excess of males. The median creatinine at presentation was 812 μmol/l, and the myeloma stage was IIIB in 44 patients. Nearly half of the patients had either light-chain or IgD myeloma, and over 90% had a detectable urinary paraprotein. Four patients with a history of treated myeloma (range 3–9 years) were referred because of slowly progressive or acute-on-chronic deterioration in renal function. Renal failure was the presenting problem in 28/52 (54%), and 75% of the patients were diagnosed as having myeloma within a period of 30 days before or 30 days after their referral with renal failure. Precipitants that may have contributed to the onset of renal failure were identified in 24 patients and are summarized in Table 3. Hypercalcaemia and the consumption of a non-steroidal anti-inflammatory agent were the most

Table 1 Metabolic and personal data on all patients

Age (years)	67 (42–82)
Sex (M:F)	32:24
Creatinine (μmol/l)	811 (302–2600)
Albumin (g/l)	35.6 ± 6.8
Calcium* (mmol/l)	2.49 ± 0.33
Haemoglobin (g/dl)	9.4 ± 2.1
WCC ($\times 10^9$/l)	8.6 ± 3.9
Platelets ($\times 10^9$/l)	222 ± 116
Myeloma stage (IIIB/IIB)	44/12
Immunoparesis**	51/56 (91%)
Osteolytic bone lesions	37/51 (73%)
Bone-marrow plasma cells (%)	43 ± 26
Urgent dialysis (<24 h)	26/56 (46%)
Ever dialysed	47/56 (84%)
Plasma-exchanged	17/56 (30%)

Results are means (SD), medians (ranges) or numbers (percentage). *Calcium was corrected to an albumin of 40 g/l. **Immunoparesis, reduced concentration of other immunoglobulin classes.

Table 2 Paraprotein (PP) data for all patients

Serum paraprotein	Serum PP level (g/l)	Serum PP subclass (*n*)	Urine PP detected*
IgG	26.1 ± 16.6	IgG (1)**	1
(*n* = 19) (34%)		IgG kappa (10)	10
		IgG lambda (8)	5
IgA	23.8 ± 18.5	IgA (1)**	0
(*n* = 11) (20%)		IgA kappa (5)	5
		IgA lambda (5)	4
IgD (*n* = 4) (7%)	13.5 ± 6.8	IgD lambda (4)	4
Kappa/lambda light chain only	3.5 ± 4.2	Kappa (9)	8
(*n* = 22) (39%)		Lambda (11)	11
		Unspecified (1)	1
		None	1 (kappa)

* Three patients had no detectable urinary paraprotein, and three were not examined for the presence of a urinary paraprotein. ** Light-chain component not specified.

Table 3 Factors identified as possible precipitants of renal failure at presentation

Factor	n (%)
None	32 (57%)
Hypercalcaemia	13 (23%)
NSAID	6 (11%)
Hypercalcaemia and NSAID	1
Sepsis	2
Dehydration/hypotension	2

NSAID, non-steroidal anti-inflammatory drugs.

commonly identified potential precipitants. The mean calcium (corrected to an albumin of 40 g/l) in those classified as hypercalcaemic requiring specific therapy ($n = 14$) was significantly higher than in those without (2.76 ± 0.51 vs. 2.40 ± 0.15 mmol/l, $p < 0.0005$), however, the mean calcium remained within the normal range (2.20–2.65 mmol/l) despite the severe renal impairment. Twenty-two patients underwent percutaneous renal biopsy. The biopsies were reported as being typical of myeloma cast nephropathy in 16, and showed an interstitial nephritis consistent or suggestive of myeloma in five. One biopsy was reported as near-normal in a patient with hypotension and no detectable urine paraprotein.

Chemotherapy

The decision to initiate chemotherapy was made independently by the haematologist (TL) and based upon clinical and laboratory parameters. Different chemotherapeutic regimens were used in the period reviewed. Eleven patients never received chemotherapy (severe acute co-morbidity or severe infection, $n = 8$; lack of symptomatic disease complications except for renal failure, $n = 1$; severe chronic co-morbidity and poor quality of life prior to myeloma, $n = 2$). Twenty-four patients (43%) received either or both of melphalan and intermittent corticosteroid at some time in their illness. Seven received vincristine, adriamycin and dexamethasone (VAD) and the remaining 14 (25%) received other cytotoxics including intravenous or oral cyclophosphamide, other combined therapies using differing combinations of vincristine, adriamycin, BCNU and prednisolone/dexamethasone, or were switched between regimens due to side-effects. The median survival of patients who never received chemotherapy was 53 days compared with 353 (Melphalan), 310 (VAD) and 262 (other), $p < 0.05$.

Dialysis

Forty-seven (84%) patients were dialysed at some time, 26 (55%) within 24 h of referral. The first modality was haemodialysis or haemofiltration in all patients. The characteristics and survival of patients who were established on chronic dialysis therapy (defined as never recovered renal function) is shown in Table 4. Patients never dialysed, excluding the two patients who received no active therapy, and those who recovered renal function, are shown as chronic renal failure (CRF). The groups differed only in their initial creatinine, and there was no significant survival difference according to treatment modality, after excluding deaths within 30 days of referral.

Recovery of renal function and plasma exchange

The seven patients who recovered renal function included two who made delayed recovery at 6 and 12 weeks, whilst the other five required dialysis for < 2 weeks. A precipitant was identified in five (71%)

Table 4 Characteristics of 54 patients according to mode of chronic renal replacement therapy

	CRF ($n=14$)	HD ($n=23$)	CAPD ($n=17$)	p
Age	61	70	65	NS*
Creatinine	481	830	995	<0.001*
Albumin	35.8±6.4	35.1±9.4	37.9±5.1	NS
Plasma-exchanged (*n*)	5 (36%)	7 (32%)	5 (29%)	NS
Plasma cell infiltrate %	42±21	48±29	33±23	NS
Chemotherapy (*n*)	13 (93%)	17 (74%)	11 (65%)	NS
Sepsis episodes (*n*)	4 (29%)	12 (55%)	15 (88%)	<0.005
Survival after first 30 days	484	236	281	NS*

Comparison of means or medians by ANOVA or * KW-ANOVA, and groups by χ^2 analysis.

compared with 14/40 (35%) in those who did not recover, and 5/9 (56%) of those never dialysed ($p=$ NS). Renal biopsy showed no significant histological abnormality in one patient, and features consistent with an acute interstitial nephritis with casts, but without extensive fibrosis or tubular atrophy, in two patients. Seventeen patients (14 requiring dialysis) received plasma exchange (median number of treatments 5, range 3–15). Three of the 14 dialysis-requiring patients recovered sufficient function to cease dialysis and the three patients specifically plasma-exchanged in conjunction with initiation of chemotherapy for deteriorating renal function all showed stabilization and improvement in creatinine.

Infection

Twenty-four patients had no infectious complications, one had insufficient documentation to classify, and 31 (55%) had a significant infection, defined as the need for antibiotic therapy based upon clinical or microbiological criteria, although this was sometimes withheld when infection was a terminal event. Of these, 13 were early, i.e <90 days, 12 had late infections (>90 days), and six patients had both early and late infections. Ten patients had CAPD peritonitis (range 1–9 episodes), eight had pulmonary infections (in 5 a terminal event), five patients had septicaemia (one fatal) and eight patients had temporary haemodialysis-catheter-related sepsis. Three patients had visceral perforations causing fatal abdominal sepsis.

Survival

The median survival of all patients was 244 days. The survival of the 54 patients actively treated is shown in Figure 1 (median survival 256 days). One third of the patients died within 90 days of referral. Excluding patients who died within 90 days of referral, the median survival was 432 days (14 months). In order to examine further the characteristics affecting the survival of the 54 patients, they

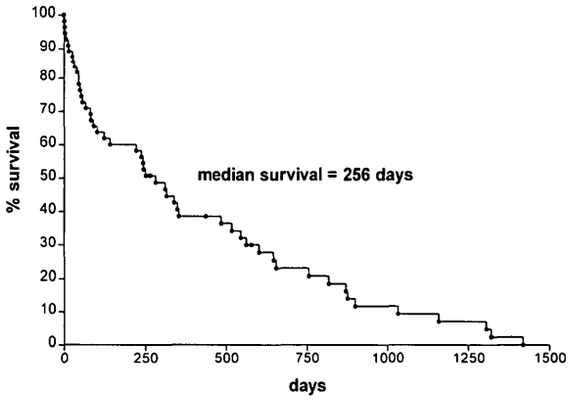

Figure 1. Survival for 54 patients with myeloma and renal disease.

were divided into tertiles of survival, and their characteristics are shown in Table 5. There was no difference in age, paraprotein class, creatinine, the percentage of plasma cell marrow infiltrate, hypercalcaemia or need for dialysis at presentation between the groups. Albumin was significantly lower in those who survived less than 90 days, and platelet count higher in those who survived >1 year. The number of patients who received any chemotherapy increased according to tertiles of survival. In a stepwise multiple regression with survival as the dependent variable and albumin, creatinine, myeloma stage, paraprotein type, platelet count, need for urgent dialysis, sepsis <90 days and age at presentation as the independent variables, only albumin and platelet count (F to remove 9.6 and 5.0 respectively, $r^2=0.21$, df=53) remained as significant predictors of survival.

Cause of death

The cause of death was unknown in two patients. Autopsies were rarely performed, so the cause of death is based upon the clinical diagnosis. We have divided cause of death into three categories: (i) due predominantly to the effects of myeloma, including withdrawal of treatment and morbidity (but not

Table 5 Characteristics of patient groupings according to tertiles of survival

Survival (days)	0–90 ($n=18$)	91–365 ($n=17$)	>365 ($n=19$)	p
Age	70	69	61	0.10
Creatinine (referral)	796	776	821	NS
Albumin	32.2 ± 6.8	38.1 ± 7.5	38.4 ± 6.7	<0.05
Platelets	185 ± 106	191 ± 127	272 ± 106	0.02
Hypercalcaemia	5 (28%)	5 (29%)	4 (21%)	NS
%PC infiltrate*	46 ± 29	44 ± 26	36 ± 22	NS
Required dialysis	17 (94%)	15 (88%)	15 (79%)	NS
Infection <90 days	8 (44%)	5 (29%)	6 (32%)	NS
Infection (total)	8 (44%)	11 (65%)	12 (63%)	NS
Chemotherapy	12 (67%)	12 (71%)	19 (100%)	<0.05

* The percentage of plasma cell infiltrate in bone marrow.

infection) e.g. cachexia, severe bone disease, spinal cord compression, including the two patients not offered supportive therapy, $n=24$; (ii) infection as the primary or a significant contributory event, ($n=14$); and (iii) other causes, e.g. sudden (presumed cardiac) death ($n=5$), and one each of acute myocardial infarction, thrombotic stroke and peripheral ischaemia, restrictive cardiomyopathy, cardiac and hepatic failure with no cause established, and disseminated urothelial tumour (total $n=10$).

Discussion

The striking discrepancy in patient referral between the periods 1980–1987 and 1988–1994 in this study is unlikely to reflect an increased incidence of myeloma during this period, but may be explained by a national under-referral of the elderly with renal failure, compounded by the perception that renal failure and myeloma represented a particularly poor prognosis during the early 1980s.

The median survival of this selected population with both severe renal failure and myeloma was only 8 months. After excluding the one-third of patients who died within the first 3 months, median survival increased to 14 months. The prevalence of light chain and IgD myeloma was increased, and nearly all the patients had Bence-Jones proteinuria, consistent with previous reports of their association with significant renal damage.[9,10] Patients without hypercalcaemia requiring treatment still had a preserved corrected calcium, suggesting that increased bone turnover due to osteoclast activity prevents the acute hypocalcaemia typically associated with other causes of acute renal failure.[16] This feature may alert physicians to the possibility of myeloma-induced acute renal failure.

Studies of unselected populations have given conflicting results of the effect of renal failure of any degree at presentation upon survival. Alexanian *et al.*[4] have suggested that renal failure at presentation does not adversely affect outcome whilst both Rayner *et al.*[7] and MacLennan[17] showed that increased creatinine at presentation independently predicted poor survival, even with improvement in creatinine levels following treatment. Our patients reflect the extreme end of the spectrum of renal impairment in myeloma, as the majority required dialytic support. Myeloma stage was advanced in 79%, and over half presented as uraemic emergencies. We compared this study with survival data from nine other series of myeloma and severe renal failure (Table 6), which showed that the range of survival varied from 4 to 22 months (median 9.5).[11–13,15,18–22] Rota *et al.*[13] reported that recovery of renal function would allow survival close to that of myeloma patients without renal failure. Pasquali *et al.*[21] identified hypercalcaemia, early infection and interstitial fibrosis on renal biopsy with a poor outcome, but not tumour stage. Ganeval *et al.*[22] identified response to chemotherapy,

Table 6 Median survival in patients with severe acute renal failure requiring dialysis 1986–1996

Series (year)	Patients (n)	Median survival (months)
Cavo (1986)	26	4
Rota (1987)	34	19
Pozzi (1987)	50	10
Misiani (1987)	23	9
Iggo (1989)	23	12*
Pasquali (1990)	37	9
Johnson (1990)	21	22
Ganeval (1992)	80	20
Torra (1995)	30	8 (20**)
Irish (1997)	56	8
Median (range)	(380)	9.5 (4–22)

* Excludes patients who recovered renal function or survived less than 1 month. ** Excluding 10 patients who died in first 2 months.

disease stage and creatinine at 1 month as predictors of survival. The reasons for the differing survival data between studies are uncertain, but differences in patient selection, definition of renal failure, treatment protocols, use of plasma exchange and requirement for dialysis are likely to be important. In agreement with some studies,[12,15] we could not show that the type of myeloma, need for urgent or long-term dialysis, or infection significantly affected survival, although the latter may have a profound effect on morbidity and quality of life. Although Pasquali *et al.*[21] have shown that early infection adversely affected outcome, we found a trend for an increased incidence in early infection only in the group that survived <3 months.

Survival in myeloma is principally determined by response to chemotherapy and the acquisition of a stable or plateau phase.[2,5] Whilst the response rate of various therapeutic regimens and their effect upon survival is still being studied, entering a stable disease state is critical to survival. The use of chemotherapy in this study was associated with longer survival, although no significant survival advantage between the various therapeutic regimes was identified. There was considerable heterogeneity in the use of chemotherapy over the 15-year period of this study, and no myeloma group without renal failure was available to use as controls, making any further comparison difficult. It is possible that the patients reported in this study may have been under-treated in comparison with other patient groups without renal failure, in part due to concern over the toxicity of chemotherapeutic drugs in advanced renal failure, particularly melphalan, and the dose or duration of treatment was frequently attenuated. Some of the patients who did not receive chemotherapy in this study were extremely ill at presentation, and a decision was made to defer treatment until their general condition was improved by dialysis, control of infection and nutrition. The delay in initiating chemotherapy could have reduced their chance of longer survival, but so might the side-effects of such treatment. The finding of a reduced plasma albumin concentration in the group who survived <90 days could indicate that it included patients with a high tumour burden and therefore needing immediate chemotherapy. Albumin is a negative acute-phase protein, and its concentration is likely to be related to the effect of interleukin–6 which, in addition to mediating the acute-phase response,[23] is a growth factor for plasma cells. Interleukin–6 concentration and its marker protein, CRP, are correlated with disease severity and patient survival.[24] The high platelet count in those who survived more than a year suggests that these patients had a lesser degree of marrow invasion at the time of presentation.

More than one half of the patients had at least one significant infectious event, and 25% of deaths were related to infection, usually pulmonary or intra-abdominal. Immunodeficiency is a feature of myeloma, and nearly all the patients in this study had profound immunoparesis of all immunoglobulin classes, predisposing them to bacterial infection and impaired mucosal immunity. The invasive nature of renal replacement therapy requiring indwelling venous catheters and the use of peritoneal dialysis catheters provides opportunities for direct bacterial invasion. Stable myeloma patients without renal failure undergoing chemotherapy and supported with regular prophylactic immunoglobulin therapy have significantly reduced morbidity from infection.[25] The use of replacement immunoglobulin therapy should be considered in the renal failure population to reduce morbidity from infectious complications. There was no survival difference between patients managed with CAPD or haemodialysis (HD), although the CAPD population had a significantly higher prevalence of infection, largely explained by CAPD peritonitis, consistent with other reports.[26,27] Whilst CAPD may provide better clearance of light chains than HD, this has not been shown to influence recovery of renal function,[28] and the further loss of immunoglobulin may be a disadvantage. One report[26] questioned the safety of CAPD as a long-term modality whilst another could find no difference in survival between HD and CAPD.[15] The evolution of CAPD technique, and especially the introduction of disconnect systems, have reduced the risk of infection, and the selection of maintenance dialysis modality for patients with myeloma and chronic renal failure should be based on the usual factors, including patient preference.

Only seven patients who required dialysis recovered renal function and in five of these some precipitant was identified. The majority of patients presented as uraemic emergencies, and the diagnosis of myeloma was made some days later. Aggressive rehydration and forced diuresis would have been inappropriate, except in the few patients with an established diagnosis of myeloma referred because of progressive renal failure. All of these patients were stabilized and dialysis was avoided in all after a combination of rehydration, plasma exchange and chemotherapy. Once patients became oliguric and dialysis-dependent, the chance of recovery of renal function was small, although other studies have reported better recovery of renal function.[13,21,22] The role of plasma exchange in myeloma and renal failure remains controversial, with some reports suggesting significant recovery from dialysis-dependence with the use of plasma exchange in addition to conventional treatment.[11,29] Three of the patients in this study who recovered renal function received

plasma exchange, but four patients recovered independently of plasma exchange. All of the patients who recovered however, received chemotherapy. The role of plasma exchange in dialysis-dependent patients requires further assessment in a large multicentre trial, as there is evidence to suggest that the absence of extensive fibrosis and tubular atrophy on biopsy may predict a beneficial response.[28]

In summary, these data suggest that the presence of severe renal failure and myeloma carries a poor prognosis. However one-third of patients survived >1 year, suggesting that treatment is worthwhile. The use of dialysis did not determine survival, which was improved by or related to the use of chemotherapy, but influences morbidity. Early diagnosis, avoidance or reversal of precipitating factors, and prompt referral to specialist centres before oliguria and dialysis is required, is essential to maximize the chance of avoiding the extra morbidity, expense and reduced quality of life that chronic dialysis entails. However, many patients, often elderly, will continue to present as uraemic emergencies, and for some the combination of myeloma and renal failure will inevitably be rapidly fatal. A low plasma albumin and platelet count at presentation may identify a group with poor prognosis due to increased tumour load. Improved chemotherapy regimens and evaluation of optimal dosage and timing in patients with severe renal failure, additional supportive measures to prolong and improve the quality of life such as immunoglobulin replacement, and early identification of patients who may benefit from aggressive plasma exchange may be required to improve renal and patient survival. Controlled studies are limited and few individual centres will be referred enough patients to provide these data emphasizing the need for multicentre studies.

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