CLINICAL RESEARCH

Should patients with renal failure associated with myeloma be dialysed?

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Abstract

In a study of renal function in multiple myeloma seven patients presented with renal failure and three developed it 16-106 months after diagnosis. All were dialysed. Infection with dehydration was a precipitating factor in all seven cases of acute or acute on chronic renal failure. Of these, two patients recovered normal renal function and one other was left with permanent renal impairment but no longer required dialysis.

Results from the seven patients with acute renal failure and for the three with more chronic features support the practice of dialysis for all patients who present with renal failure. Dialysis is not indicated for those patients with progressive myelomatous disease. The study showed no evidence that chemotherapy permitted recovery from established renal failure. The prognosis in this elderly group is heavily dependent on the presence of cardiovascular or other degenerative disease.

Introduction

Historically, renal failure is second only to infection as the most common cause of death in multiple myeloma.[1] Renal insufficiency occurs in 55% of patients at presentation[1] and has been associated with a poor prognosis.[1 2] The recent use of high fluid regimens has improved the prognosis[3] but there is still a high incidence of renal impairment. With the increasing availability of facilities for dialysis deaths attributable to myeloma associated uraemia might be preventable.[4 5]

There have been several case reports of myeloma associated renal failure being treated by short term dialysis, accompanied

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by chemotherapy or plasmapheresis, which permitted the recovery of sufficient renal function for prolonged survival.[6-8] In two series of 20[9] and 24[5] patients collected over 13 and 10 years, however, only four patients recovered renal function. Both series were retrospective and, since the results were influenced by changing treatment regimens over the long periods in which data were collected, a new evaluation is needed.

As part of a larger, prospective study of renal function in multiple myeloma, we set out actively to treat all patients with severe renal failure in order to define criteria for selecting those likely to benefit from dialysis. We tried to answer three questions: Are there patients with life threatening acute renal failure who can be rescued by short term dialysis so that they can then be treated for myeloma? Can chemotherapy for myeloma improve renal function in patients with chronic renal failure? Irrespective of the effect of chemotherapy on renal failure, is it justifiable to use long term dialysis to keep such patients alive?

Patients and methods

During July 1980 to September 1982, 45 patients entered our myeloma renal study, of whom 19 had some degree of renal impairment (serum creatinine concentration over 150 μmol/l (1·7 mg/100 ml)). This paper reports on the subgroup of 10 patients with severe renal failure who required dialysis. Table I lists the indications for dialysis in the 10 patients. In all cases we considered that withholding dialysis would have resulted in death. All patients had multiple myeloma based on criteria of the Medical Research Council (fourth trial), each possessing at least two of the following three factors: paraprotein in serum or urine; lytic skeletal lesions; plasma cell infiltration in the bone marrow.

All patients had intermittent (monthly, dependent on blood count) chemotherapy with oral melphalan (10 mg for two to five days) and prednisolone (40 mg daily for three to seven days), three patients (cases 1-3) also receiving intravenous vincristine 1 mg. Two patients (cases 9 and 10) were given "second line" treatment with intravenous carmustine and doxorubicin (Adriamycin) 30 mg/m², while in case 8 the patient also had two 3 litre plasma exchanges two weeks before he died.

Six cases (1, 3, 6, 8, 9, and 10) were categorised as "acute" or "chronic" renal failure according to the biochemical results within a month before the episode of severe renal failure. Though previous biochemical results were not available, a short history with complete

recovery of renal function supported the diagnosis of acute renal failure in case 2. Three patients (cases 4, 5, and 7), categorised as chronic renal failure all had a history of several months of progressive lethargy and anorexia before presenting with severe uraemia and anaemia (see table II). These patients did not recover renal function.

Percutaneous renal biopsy was performed in seven cases (1, 2, 3, 4, 5, 6, and 10) within a month of presentation with renal failure; in one other patient (case 9) biopsy had been performed one year previously, when creatinine clearance was 45 ml/min and a light chain proteinuria of 1 g/24 hours had been recorded. The degree of tubular atrophy and cast formation in the seven biopsy specimens was graded for severity on a five point scale by a histologist unaware of other parameters of renal function.

Urine and serum samples were taken after rehydration and before dialysis. Urine free light chains were measured by radioimmunoassay.[10] Because of the small numbers we were unable to assume a normal distribution of values. Groups were therefore compared by the non-parametric two tailed Mann-Whitney U test.

Results

CLINICAL, BIOCHEMICAL, AND BIOPSY FINDINGS

In the group as a whole presenting signs and symptoms were those of uraemia without hypertension. Infection was present in all seven cases of acute or acute on chronic renal failure; one patient (case 3) had also undergone intravenous pyelography two weeks before admission. Bone pain and hypercalcaemia (calcium concentration over 2·7 mmol/l (10·8 mg/100 ml)) correlated with evidence of extensive lytic skeletal lesions and was present in four patients (cases 2, 7, 8, and 9) (table II).

All patients (except case 6 with amyloid) had light chain proteinuria (>150 mg/l) (table II).

"Myeloma kidney" with dense laminated tubular casts and cellular atrophy occurred with varying severity in all biopsy samples, including

that from case 6 with glomerular amyloid deposits. Cast formation was more pronounced in chronic renal failure, though the numbers were small.

PROGNOSIS

Tables III and IV show the outcome in the 10 patients. There were seven deaths. Long term dialysis was discontinued in two patients—in case 8 because of extensive amyloid polyneuropathy and in case 7 because of severe technical problems; in this patient treatment was ended after discussion with the family. There were no significant differences between patients with acute and chronic renal failure in age, sex, paraprotein type, serum calcium and urinary light chain concentrations, and 24 hour amount. The haemoglobin concentration was higher in patients with acute renal failure than in patients with chronic renal failure ($U = 0$; $p < 0.02$).

The two patients (cases 1 and 2) whose renal function recovered and who had a prolonged survival had both had acute renal failure, a comparatively low urinary light chain concentration, and relatively mild tubular atrophy and cast formation on renal biopsy (table II). These two patients show that short term dialysis for acute renal failure of multiple myeloma is life saving and may result in recovery of renal function. Three other patients (cases 3, 9, and 10) also had acute renal failure but showed no recovery of renal function and had a poor prognosis, related to a high tumour load (cases 9 and 10) and ischaemic heart disease (case 3). Of the five patients with chronic renal failure, only one (case 6) showed any recovery of renal function; the slight improvement (creatinine clearance becoming stable at 12 ml/min) may, however, have represented treatment of the acute dehydration rather than recovery of renal function in response to chemotherapy. Three of these patients (cases 5, 7, and 8) were kept alive for prolonged periods by dialysis. All died; only one death was attributable to the underlying myeloma (case 8). The others died of cardiac failure (case 5) and uraemia due to discontinuation of dialysis (case 7).

TABLE I—*Details of patients and indications for dialysis*

Case No	Diagnosis*	Sex	Age	Renal failure	Time from diagnosis of renal failure (months)	Predialysis biochemical values			Indications for dialysis
						Urea (mmol/l)	Creatinine (μmol/l)	Potassium (mmol/l)	
1	IgA lambda	M	60	Acute	0	76	1139	5·3	Uraemia
2	IgG lambda	F	48	Acute	0	43	1500	7·4	Fluid overload, rising potassium
3	IgA lambda	M	55	Acute	0	50	1400	7·0	Fluid overload, uraemia
4	Free kappa	F	70	Chronic	0	52	1800	5·4	Fluid overload, uraemia
5	IgA lambda	F	61	Chronic	0	100	2600	4·9	Uraemia
6	IgG kappa	F	70	Acute on chronic	0	73	1320	8·2	Uraemia, acidosis, rising potassium
7	IgG kappa	M	66	Chronic	0	60	2000	6·0	Uraemia
8	Free lambda	M	57	Acute on chronic	16	52	1940	3·6	Fluid overload, uraemia
9	Free lambda	F	62	Acute	19	28	657	5·4	Fluid overload
10	IgG kappa	M	47	Acute	106	71	1247	7·2	Uraemia, rising potassium

* Lambda and kappa refer to light chain subtypes.
  Conversion: SI to traditional units—Urea: 1 mmol/l ≈ 6 mg/100 ml. Creatinine: 1 μmol/l ≈ 0·01 mg/100 ml. Potassium: 1 mmol/l = 1 mEq/l.

TABLE II—*Presenting features before dialysis of 10 patients with multiple myeloma*

Case No	Renal failure	Precipitating factor	Symptoms	Oliguria	Blood pressure (mm Hg)	Haemo-globin (g/dl)	Calcium (mmol/l)	Plasma cells in bone marrow (%)	Lytic lesions on skeletal survey	Casts on renal biopsy*	Urinary light chain (mg/l)	Serum paraprotein Ig (g/l)
1	Acute	Septic arthritis	Uraemia	No	110/85	13·1	1·9	25	Negative	1	190	34
2	Acute	Chest infection	Uraemia	No	160/80	9·8	2·7	22	Multiple	2	600	26
3	Acute	Renal colic, urinary tract infection	Uraemia	No	160/80	12·2	2·1	75	Negative	3	1100	24
4	Chronic		Bone pain, uraemia	No	200/90	5·6	2·4	40	Extensive	3	1250	
5	Chronic		Uraemia	No	115/70	5·7	2·2	40	Extensive	4	1800	2
6	Acute on chronic	Chest infection	Uraemia	No	170/90	7·4	1·7	8	Negative	3	61	20
7	Chronic		Bone pain, uraemia	No	140/80	6·1	2·7	75	Isolated		2500	2
8	Acute on chronic	Pancreatitis, chest infection	Bone pain, uraemia	No	140/80	10·5	4·0	27	Extensive		587	
9	Acute	Chest infection	Bone pain, uraemia	Yes	130/50	7·3	3·5	80	Extensive	(2)†	2500	
10	Acute	Chest infection	Bone pain, uraemia	Yes	120/80	7·9	2·4	75	Extensive	2	4000	37

* Renal biopsy classified 0-4 for severity of casts (see methods).
† Biopsy done one year before acute renal failure.
  Conversion: SI to traditional units—Calcium: 1 mmol/l ≈ 4 mg/100 ml.

TABLE III—*Dialysis and outcome in 10 patients with multiple myeloma*

Case No	Type of dialysis	Duration of dialysis	Recovery of renal function	Survival	Response to chemotherapy*	Cause of death
1	Peritoneal	1 week	Yes	>18 months	Yes	Alive
2	Peritoneal	1 week	Yes	>33 months	Yes	Alive
3	Peritoneal	1 week	No	1 month	No	Cardiac failure, ischaemic heart disease
4	Intermittent peritoneal	1 month	No	2 months	Yes	Myocardial infarction
5	Intermittent peritoneal	6 months	No	6 months	Yes	Cardiac failure, ischaemic heart disease
6	Peritoneal	1 week	Slight	>7 months	Yes	Alive
7	Continuous ambulatory peritoneal and haemodialysis	2 months, 2 weeks	No	2 months	Yes	Uraemia, dialysis discontinued
8	Peritoneal and haemodialysis	1 week × 2,4 months	No	24 months	Yes	Uraemia, amyloid neuropathy
9	Peritoneal	1 week	No	1 week	No	Chest infection, progressive disease
10	Peritoneal	1 week	No	1 week	No	Chest infection, progressive disease

* Positive response to chemotherapy judged by >50% reduction in paraprotein concentration or urinary light chains.

TABLE IV—*Summary of outcome in seven patients who presented with renal failure and in three whose renal failure developed during disease. (Case numbers in parentheses)*

Renal failure	No of patients	Outcome
Patients with renal failure on presentation (1-7)		
Acute	3	2 recovered renal function, were alive at 18, 33 months (1,2) 1 died at one month (3)
Acute on chronic	1	alive, off dialysis at seven months (6)
Chronic	3	1 died at two months (4) 1 died at six months (5) 1 died at two months (7)
Patients whose renal failure developed during disease (8-10)		
Acute	2	died at one week (9, 10)
Acute on chronic	1	died at eight months (8)

Discussion

Several factors have been implicated in myeloma associated renal damage. Our results confirm the clinical association[4] between free urinary light chains and renal failure. Animal[11] and clinical[4] studies have shown that, in myeloma, dehydration or desalination contributes to acute renal failure; appropriate fluid repletion alone (without change in tumour load) can produce a diuresis with improvement in renal function.[3] Hypercalcaemia (>2·7 mmol/l; > 10·8 mg/100 ml) occurs in 30% of all patients with myeloma,[1] and was present in 40% of our series; alone it may result in such tubular dysfunction as impaired urinary concentration and so cause dehydration. Infection is a presenting factor in 14% of patients[1] and was present in 70% of our series. This may be related to the impaired cellular[12] and humoral immunity[13] that occurs in myeloma and may aggravate any associated dehydration. The occurrence of acute renal failure after intravenous pyelography in myeloma is well recognised but the mechanism of damage is controversial[4 14]; this factor could be implicated in only one of our patients (case 3). DeFronzo et al[4] conducted a retrospective study of 14 patients with myeloma who developed acute renal failure and found precipitating causes in 12—seven had become hypercalcaemic, three had been given nephrotoxic antibiotics, and two had fluid depletion. All seven of our patients with acute renal failure had precipitating factors (table II).

One postulated consequence of severe fluid depletion is reduced urinary flow with high light chain concentration and cast formation, intrarenal obstructive nephropathy, and secondary tubular atrophy. In all the biopsies in our series, however, the predominant finding was tubular atrophy; indeed, cast formation was less pronounced in acute than in chronic renal failure. It has been suggested[7 15] that the degree of renal impairment correlates better with tubular atrophy than with the presence of obstructive casts, observations which would be consistent with animal and in vitro evidence that some light chains damage renal tubular cells.[16 17] The primary determinant of renal damage by a given light chain seems likely to be its toxic effect on tubular cells. Extensive cast formation may be a later phenomenon.

In one retrospective study of 14 patients with acute renal

failure[4] only a single patient survived for more than two months; in another of eight patients treated by short term peritoneal dialysis[9] seven died within two months. These studies reflect uraemic deaths, for long term dialysis facilities were not available. In the Mayo Clinic series[9] of acute and chronic renal failure only two out of 20 patients recovered renal function. These disappointing figures show that the correction of such factors as hypercalcaemia and hypovolaemia combined with short term dialysis does not ensure recovery of renal function, and we found no evidence that chemotherapy for myeloma permitted improvement in the level of renal function.

Prognosis in myeloma is related principally to tumour mass,[18] and this is reflected in the survival of patients who have been dialysed. Cosio et al[5] in a personal series of 24 patients collected over 10 years and a review of published work on a further 19 cases (biased towards successful treatment) found no difference in survival for acute or chronic renal failure in patients treated by long term haemodialysis, the one year survival being 53%. This is far below the expected survival with dialysis of patients who do not have myeloma, and comparable to the 66% for patients with myeloma who do not have renal failure.[5] If our patients are classified according to Durie and Salmon's staging system for tumour mass[18] (excluding haemoglobin values), two (cases 1 and 2) had low tumour mass and a good prognosis. Each would have died without dialysis; both recovered from renal failure and were alive at 18 and 33 months. By contrast, two patients (cases 9 and 10) had massive tumour loads and a poor prognosis independent of renal failure. Despite dialysis both died within a week.

An important feature of our series was the incidence of death unrelated to multiple myeloma (table III). This underlines the degeneration to be expected in this elderly group.

We believe that all patients presenting with acute renal failure and myeloma should be dialysed. Long term haemodialysis or continuous ambulatory peritoneal dialysis should be considered only for patients with chronic renal failure and myeloma responsive to chemotherapy. In determining whether or not to institute this treatment the extent of other systemic or degenerative diseases must be considered. Patients who develop renal failure gradually and who have progressive myeloma unresponsive to chemotherapy should not be dialysed, for the prognosis is very poor.

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Comparison of human versus porcine insulin in treatment of diabetes in children

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Abstract

The blood glucose control obtained when using semi-synthetic monocomponent human insulin (insulin A) was compared with that using standard monocomponent porcine insulin (insulin B) in 14 children in a double blind crossover study. At the start of the study age, duration of diabetes, insulin dose, and daily carbohydrate intake were the same in both groups. After a one month run in period of standard treatment with porcine insulin the children were randomly divided into group 1 (three months of insulin A followed by three months of insulin B) and group 2 (three months of insulin B followed by three months of insulin A). During each treatment period blood glucose control was assessed by clinical symptoms, glycosylated haemoglobin, and home blood glucose monitoring.

Although a significant difference in the period after lunch during 24 hour blood glucose profiles suggested a shorter onset time and faster peak action time of human insulin, no significant difference in the overall diabetic control was seen between the two types of insulin. There was a trend towards improved blood glucose control (irrespective of insulin) as the trial progressed. No clinical reactions to human insulin occurred, and there was no significant difference in the daily insulin dose between porcine and human insulin.

Introduction

The final stage in the development of pure insulin is now complete with the introduction of human insulin. A protein with an amino acid sequence identical with that of naturally occurring human insulin can be manufactured either bio-synthetically by DNA recombinant techniques[1] or by chemical modification of porcine insulin. In the latter process the terminal amino acid of the β chain of the porcine insulin is substituted by a chemical enzymatic technique replacing alanine with threonine.[2]

We report a clinical trial comparing the effects of chemically modified semisynthetic monocomponent human insulin and monocomponent porcine insulin on blood glucose control in a group of diabetic children.

Patients and methods

Seventeen children were originally selected for the trial. Informed consent was obtained from the children and their parents and the study protocol approved by the hospital's ethics committee. Three children were unable to complete the trial owing to failure to comply with the data collection. All the children were treated with either human monocomponent Monotard and Actrapid insulin (A) or porcine monocomponent Monotard and Actrapid insulin (B) (Novo). The trial had a double blind, crossover design and began with a one month run in period. During the run in period subjects continued with monocomponent porcine insulin and every effort was made to optimise blood glucose control. The children were then randomly allocated to group 1 (three months of insulin A, changing to three months of insulin B; n=8) and group 2 (three months of insulin B, changing to three months of insulin A; n=6). Twelve of the 14 children were treated with a once daily regimen of Actrapid and Monotard, and one child in each group was treated with a twice daily regimen of Monotard and Actrapid insulin.

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