STEROID PULSES AND PLASMAPHERESIS IN THE TREATMENT OF ACUTE RENAL FAILURE IN MULTIPLE MYELOMA

F Locatelli, C Pozzi, L Pedrini, P Marai, S Di Filippo, R Ponti, R Costanzo

Divisione di Nefrologia e Dialisi, Ospedale di Lecco, Italy

Summary

Four patients with acute renal failure due to myeloma (IgG with lambda, lambda, lambda, IgG with kappa) were studied; serum creatinine was 4.7, 5.9, 4.25, 10.8 mg%, and proteinuria 2.1, 2.8, 5.2, 4.2g/24h respectively. Renal biopsy specimens (3 patients) showed interstitial fibrosis, oedema, infiltration of mononuclear cells, tubular atrophy or dilatation with many ‘myeloma kidney’ casts.

The patients were treated with plasmapheresis (2–4 exchanges) and methyl-prednisolone pulses (three to four 1g pulses). Maintenance therapy included prednisone, vincristine, melphalan and cyclophosphamide.

After a follow up of 26, 17, 8, 6 months respectively, serum creatinine levels are 1.7, 2.4, 1.8, 4.2mg% respectively.

Proteinuria disappeared after three months of therapy in 3 patients, and then remained absent for the successive follow up.

Introduction

Renal failure is a grave prognostic sign in myelomatosis [1–5]. The mean survival is reported to be between 2 and 13 months [1,4], despite the use of dialysis and chemotherapy.

We used methylprednisolone ‘pulses’ and plasmapheresis in the treatment of acute renal failure (ARF) in myeloma and evaluated the effectiveness of this therapeutic programme not only in the acute stage, but also in a longer follow up.

Plasmapheresis has been used to remove from the body myeloma proteins [6,7,8] responsible for the tubular damage [9,10].

We have combined plasmapheresis with steroid pulses to obtain a rapid effect on the synthesis, and therefore on the excretion, of Bence Jones proteins [11].
Patients and methods

We studied four patients with ARF in myeloma (Table I).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Myeloma type</th>
<th>Proteinuria (g/24h)</th>
<th>Serum creatinine (mg%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PT</td>
<td>AT</td>
<td>3M</td>
</tr>
<tr>
<td>SA</td>
<td>IgG-λ</td>
<td>2.1</td>
<td>0.4</td>
</tr>
<tr>
<td>CA</td>
<td>λ</td>
<td>2.8</td>
<td>0.15</td>
</tr>
<tr>
<td>LU</td>
<td>λ</td>
<td>5.2</td>
<td>0.3</td>
</tr>
<tr>
<td>PG</td>
<td>IgG-k</td>
<td>4.2</td>
<td>4.3</td>
</tr>
</tbody>
</table>

In patient SA pneumonia, treated with 2.5mg/kg/day of gentamycin for 11 days, preceded the onset of ARF.

CA began to present proteinuria, with normal BUN, 1 year before admission. Bronchitis and dyspeptic symptoms preceded the onset of ARF.

In patient LU vertebral fractures, evidence of osteolytic lesions on roentgenograms of the vertebral column and pelvic bones, with progressive increase in serum calcium values up to 15.2mg%, and pneumonia preceded ARF.

Patient PG was found to have myeloma about 2 months before admission at our unit; at that time she complained of vertebral column pain, serum creatinine was 2.95mg% and the kidneys were reduced in size. Arterial hypertension was also found. Two courses of chemotherapy, including vincristine, melphalan, cyclophosphamide and prednisone had been administered. Probably dehydration enhanced the rapid impairment of renal function.

At the time of admission to our unit the serum creatinine levels in the four patients were respectively 4.7, 5.9, 4.25, 10.8mg%. Proteinuria was respectively 2.1, 2.8, 5.2, 4.2g/24h; in SA urinary protein immunoelectrophoresis showed only IgG at first, and then also lambda light chains appeared in the urine; in CA and LU only lambda light chains were found; in PG IgG and kappa light chains were found from the first observation. Only SA showed raised serum immunoglobulin levels (IgG 5500mg%) with total protein values of 8.6g%.

Hypercalcaemia was found in LU (15.2mg%); PG two months before admission showed raised serum calcium levels (12.2mg%), corrected by therapy. Three patients (SA, CA, LU) underwent renal biopsy. Histological specimens showed interstitial fibrosis (very wide in CA), associated with oedema and infiltration by mononuclear cells; many tubules were atrophic and dilated, with many myeloma casts. None of the three patients showed significant glomerular or vascular lesions. Aspirated bone marrow specimens showed massive infiltration by plasma cells in all patients; in two patients (LU and PG) atypical plasma
cells (8–10%) were found in peripheral blood samples.

Plasmapheresis was performed using the Haemonetics (mod. 30) discontinuous flow cell separator. In SA 4950ml of plasma were exchanged with fresh plasma in two sessions with 12 days interval. CA and LU underwent 3 exchanges within 15 days (respectively 7400 and 8650ml of plasma were exchanged). In PG 8850ml of plasma were exchanged in 4 sessions within 25 days.

Three pulses of methylprednisolone (1g each pulse) were administered intravenously to each patient every other day.

Particular care was taken to alkalinise the urine by giving sodium bicarbonate per os and to maintain a sustained diuresis, to prevent Bence Jones protein precipitation in the renal tubules.

PG underwent four haemodialytic sessions in the acute stage.

Maintenance therapy consisted of prednisone administration; the dosage was between 0.15 and 1mg/kg/day in relation to individual tolerance and to the contemporary chemotherapy. SA received 2.5mg/day of melphalan but the development of leucopenia induced us to stop its administration, in spite of careful dosage, and to administer one further pulse. CA received 2mg/kg/day of cyclophosphamide for the first month and then 1.3mg/kg/day for the following 11 months. LU received 1.3mg/kg/day of cyclophosphamide for one month, then the drug was stopped because of the appearance of toxic skin lesions. Two further pulses were then administered at 15 day intervals. PG had not received chemotherapy because of unfavourable haematological status; she had one further pulse because of her unsatisfactory response to the therapy.

From November 1979 we replaced this maintenance therapy with a programme of intermittent polychemotherapy which includes: 1mg of vincristine + 1g of methylprednisolone intravenously the first day, 2.5 – 5mg/day of melphalan and 75 – 100mg/day of cyclophosphamide for the following four days, 100mg/day of prednisone the third, fourth and fifth days. Cyclophosphamide was excluded in LU because of the previous development of toxic skin lesions.

These therapeutic courses were repeated at 4 – 6 week intervals, after checking the haematological status.

Results

Our results are shown in Table I. In three patients (SA, CA, LU) the treatment was successful. In SA serum IgG levels, previously elevated, came back to the normal range after 3 pulses and 2 plasmapheresis sessions, and so did the total plasma proteins. A progressive increase in IgG up to 2600mg% after 22 months follow up was corrected by polychemotherapy and pulses.

In the patient with more severe renal function impairment (PG) proteinuria did not respond to the therapy. Serum creatinine, after the acute stage, was between 3.5 and 5.2mg%.
Discussion

When renal failure occurs in myeloma the highest mean survival reported is 13 months [1,4], in spite of chemotherapy and supportive measures such as haemodialysis.

Therefore we searched for an alternative programme, bearing in mind the following important concepts:

1) The importance of the proteinuria in inducing renal failure both by deposition of myeloma proteins in renal tubules and by epithelial damage due to the hyperreabsorption [9,10].

2) The impossibility of giving high dosage chemotherapy because of the risk of bone marrow aplasia, with consequent infectious complications which can cause death. This risk is even greater in renal failure.

3) The importance of supportive therapy. In fact in the series reported by Ganeal [4] extracellular dehydration was found to be the cause of acute renal failure in 6 of 19 cases. Moreover, other events responsible for ARF in myeloma (acute infections, urography, hypercalcaemia, urate lithiasis) are often accompanied by dehydration.

All our patients showed significant proteinuria on admission.

Plasmapheresis seemed to be, in our opinion, the most rapid and effective therapy, lacking in risk of infections.

The pulses were the other aggressive therapeutic programme that we thought convenient. This way of steroid administration has been very useful, in our experience, in transplant rejection, lupus and cryoglobulinaemia, with rapid results and relatively low toxicity if we do not exceed 4–5 administrations per course. Moreover pulses have been reported to inhibit osteoclastic activity stimulated by anomalous plasma cells [12].

Proteinuria showed a good response after 2–4 plasmapheresis sessions and 3 pulses. Serum creatinine levels decreased simultaneously with the decrease in proteinuria, suggesting that renal damage could be accounted for by the nephrotoxicity of myeloma proteins.

It is noteworthy that after three months of therapy proteinuria disappeared completely in the three responsive patients, and then remained absent for the successive follow up.

It is difficult to attribute these results to the chemotherapy alone. The dosage, even in the acute stage of the illness, was kept very cautious for the reasons mentioned. This could also explain the low incidence of infectious and haematological complications in our patients.

We decided to go over to intermittent chemotherapy because this programme seems to be very convenient in the steady stage of the illness [13]; vincristine particularly seems to act on the cellular cycle, reducing tumour mass further even during remission.

In the intermittent programme we maintained the pulse administration.

We preferred to keep to low dosages of melphalan and cyclophosphamide even in intermittent courses, because of the constant risk of leucopenia, particularly in patients with renal functional impairment.

In conclusion we can say that the therapeutic programme that we adopted,
including plasmapheresis, pulses, chemotherapy at a low dosage and the other
supportive measures, particularly the maintenance of a sustained alkaline diuresis,
has resulted in good improvement in renal function with a low incidence of
adverse side effects.

Our data do not allow us to define which single measure gives such results.
Nevertheless, we think that the effectiveness of each measure is proportional
to the extent and rapidity of its effect in reducing proteinuria.

The follow up and the number of patients observed are too limited to
give conclusive judgments, but the first results are very encouraging.

Acknowledgments

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