Renal Failure in Multiple Myeloma

Presenting Features and Predictors of Outcome in 94 Patients From a Single Institution

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Background: Twenty percent of patients with multiple myeloma (MM) have renal failure.

Objective: To analyze the presenting features, the response to therapy, and the factors associated with renal function recovery and survival in 94 patients with MM and renal failure.

Patients and Methods: Medical records of patients from our institution with MM and renal failure diagnosed between January 1969 and December 1994 were reviewed. The statistical methods consisted of Kaplan-Meier survival curves, the log-rank test, logistic regression analysis, and the Cox proportional hazards model for survival analysis.

Results: Renal failure was observed in 94 (22.2%) of 423 patients. Patients with renal failure had more advanced disease than the others. Patients with renal failure had a lower response rate to chemotherapy than those with normal renal function (39% vs 56%; P<.001). However, when patients dying within the first 2 months of treatment were excluded, no significant differences in the response rate were found between patients with renal failure and those with normal renal function. Renal function recovery was observed in 26% of patients. Serum creatinine level (<354 µmol/L [<4 mg/dL]), serum calcium level (≥2.88 mmol/L [≥11.5 mg/dL]), and amount of proteinuria (<1 g/24 h) were associated with renal function recovery. Patients who recovered renal function had a median survival of 28 months vs 4 months for those with nonreversible renal failure (P<.001). In the multivariate analysis, only serum creatinine level (P = .003) and response to chemotherapy (P<.001) were correlated with survival.

Conclusions: Renal failure was present in almost one fourth of patients with MM. Patients with reversible renal failure had longer survival than those not recovering renal function. When patients dying within the first 2 months of treatment were excluded, the response rate was not affected by renal function. Factors associated with renal function recovery were degree of renal failure, presence of hypercalcemia, and amount of proteinuria. Response to chemotherapy and severity of renal failure were the only independent factors associated with survival.

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RESULTS

PATIENT CHARACTERISTICS

Renal failure was present in 94 (22.2%) of 423 patients at diagnosis. Table 1 shows the main characteristics at presentation of patients with and without renal failure. Patients with renal insufficiency had a poorer performance status, more advanced skeletal involvement, higher serum lactate dehydrogenase levels, and a higher degree of anemia and hypercalcemia. In fact, 87% of patients with renal failure were in stage III according to the system of Durie and Salmon, whereas 44.1% of patients with normal renal function had stage III myeloma. Patients with renal failure more frequently had Bence Jones myeloma than did those with normal renal function.
PATIENTS AND METHODS

PATIENTS AND DIAGNOSTIC CRITERIA

From January 1969 to December 1994, 423 patients at our institution were diagnosed as having MM. The diagnosis of MM was made following the criteria of the Chronic Leukemia–Myeloma Task Force.10 Patients with smoldering myeloma11 were not considered, and all the patients included in the study had symptomatic disease. Patients were classified according to the staging system of Durie and Salmon.12

Renal failure was defined as a serum creatinine level of 177 µmol/L or higher (≥2 mg/dL). Reversibility of renal insufficiency required a sustained decrease in the serum creatinine level to less than 133 µmol/L (<1.5 mg/dL).

TREATMENT

All patients received supportive care with hydration and transfusions when needed. Hypercalcemia was treated with forced diuresis with saline solution and furosemide plus glucocorticoids. No bisphosphonates or calcitonin were used in this phase of the disease in our patients. Chemotherapy regimens consisted of cycles of melphalan and prednisone (31 patients); cyclophosphamide and prednisone (4 patients); vincristine sulfate, cyclophosphamide, melphalan, and prednisone (VCMP; 22 patients); alternating cycles of VCMP and vincristine, carmustine, doxorubicin hydrochloride (Adriamycin), and prednisone (23 patients); and vincristine sulfate, Adriamycin, and dexamethasone phosphate (VAD; 1 patient). Seven patients received low doses of alkylating agents on a continuous basis or prednisone alone, and 6 patients received no treatment because of their extremely poor clinical condition. Alkylating agents (ie, melphalan and cyclophosphamide), as well as carmustine and Adriamycin, were usually given at half doses in the first 2 cycles of chemotherapy; if no severe myelosuppression was observed in patients who recovered renal function, the doses of these agents were increased in subsequent courses. In addition to the supportive care and chemotherapy, patients were actively treated with dialysis when needed. Thus, 34 patients received renal replacement therapy with dialysis. The characteristics and outcomes of some of the patients included in this study requiring maintenance dialysis have been reported in detail elsewhere.3 Furthermore, 9 patients were also treated with plasmapheresis.

CRITERIA OF RESPONSE TO CHEMOTHERAPY

Objective response was defined as (1) a reduction of 30% or more in the M-component size in both serum and urine, (2) a decrease of 50% or less in the size of plasmacytomas, and (3) improvement in the symptoms of bone pain and anemia and performance status, with no increase of lytic bone lesions and correction of hypercalcemia if initially present.10 Patients who fulfilled all these criteria but who did not achieve a 50% or more reduction in the M-component size were considered to have partial response or improvement. Patients who did not fulfill the criteria for objective or partial response were considered treatment failures.10

STATISTICAL METHODS

The χ2 and Fisher exact tests were used to assess the statistical significance of multiple comparisons. Survival curves were plotted according to the method of Kaplan and Meier13 and were statistically compared by means of the log-rank test.14 The multivariate analysis was performed by logistic regression15 for reversibility of renal failure and by the stepwise proportional hazards regression method of Cox for survival.16 Data were analyzed with a statistical software package (BMDP, Berkeley, Calif).

REVERSIBILITY OF RENAL FAILURE

Of 91 patients with sufficient follow-up information, 24 (26%) recovered normal renal function. The average time to renal function recovery was 1.6 months. In all except 2 of these patients, renal function was recovered in less than 4 months. Only 4 (8%) of 50 patients with serum creatinine levels of 354 µmol/L or higher (≥4 mg/dL) had reversible renal failure, whereas renal failure was reversible in 20 (48%) of 41 patients with creatinine levels lower than 354 µmol/L (<4 mg/dL). Fourteen (58%) of 24 patients who recovered renal function had hypercalcemia. In the univariate analysis, the features associated with renal function recovery were low serum creatinine level (P<.001), hypercalcemia (P=.02), amount of proteinuria (P<.001), and M-component type (Bence Jones vs others; P = .05). In the logistic regression analysis, only creatinine level (cut-off value, 354 µmol/L [4 mg/dL]; P = .001), calcium (cut-off value, 2.88 mmol/L [11.5 mg/dL]; P = .02), and amount of proteinuria (cut-off value, 1 g/24 h; P = .02) independently affected renal function recovery (Table 2).

RESPONSE TO CHEMOTHERAPY

Twenty-nine (39%) of 75 evaluable patients with renal failure responded to chemotherapy, whereas the response rate among 264 evaluable patients with normal renal function was 56.4% (P<.001). Twenty-two (29%) of 75 patients with renal failure died during the first 2 months of treatment compared with 19 (7.2%) of 264 patients without renal failure (P<.001). If patients who died within the first 2 months of initiation of treatment are excluded, there are no significant differences in the response rate between patients with renal failure and those with normal renal function. Considering only the subgroup of patients with renal failure, among 33 evaluable patients treated with a single alkylating agent plus prednisone (melphalan and prednisone or cyclophosphamide and prednisone), the response rate was 24%, whereas in 42 evaluable patients who received combination chemotherapy (VCMP; VCMP and vincristine, carmustine, Adriamycin, and prednisone; or VAD), the response rate was 50% (P=.03).

SURVIVAL

The median survival of the 94 patients with renal failure was 8.6 months, whereas that of the 329 patients with normal renal function was 34.5 months (P<.001) (Figure 1). No significant differences were found between patients treated with a single alkylating agent plus prednisone and those receiving combination chemotherapy (median survival, 12.9 vs 14.2 months; P = .93). The median survival

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of patients who recovered from renal failure was 28.3 months vs 3.8 months for those with irreversible renal failure ($P<.001$) (Figure 2). No significant differences in survival were found in patients with normal renal function vs those with reversible renal failure (median, 34.5 vs 28.3 months; $P = .97$) (Figure 3). The features significantly correlated with survival in the univariate analysis were serum lactate dehydrogenase ($P = .007$), creatinine ($P = .02$), and albumin ($P = .03$) levels; renal function recovery ($P = .004$); and response to chemotherapy ($P < .001$). However, in the multivariate analysis, only creatinine level ($P = .003$) and response to chemotherapy ($P < .001$) retained their prognostic significance.

### Table 1. Patients and Characteristics at Presentation

<table>
<thead>
<tr>
<th>Creatinine Level†</th>
<th>$&lt;177 \mu mol/L (n = 329)$</th>
<th>$\geq 177 \mu mol/L (n = 94)$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>63 (33-96)</td>
<td>63 (37-85)</td>
<td>.32</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>168/161</td>
<td>40/54</td>
<td>.16</td>
</tr>
<tr>
<td>Performance status (Eastern Cooperative Oncology Group $\geq 2$)</td>
<td>217/314 (69.1)</td>
<td>92/94 (98)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lytic bone lesions (Durie and Salmon’s scale = 3)</td>
<td>31/319 (9.7)</td>
<td>20/92 (22)</td>
<td>.003</td>
</tr>
<tr>
<td>Hemoglobin value $&lt; 90$ g/L</td>
<td>84/323 (26.0)</td>
<td>49/93 (53)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Calcium level $\geq 2.88$ mmol/L‡</td>
<td>33/307 (10.7)</td>
<td>35/91 (38)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Increased lactate dehydrogenase level</td>
<td>37/240 (15.4)</td>
<td>25/74 (34)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Clinical stage (Durie and Salmon)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>19 (5.7)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>133 (40.4)</td>
<td>11 (12)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>III</td>
<td>145 (44.1)</td>
<td>82 (87)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>32 (9.7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>M-component type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>185 (56.2)</td>
<td>35 (38)</td>
<td></td>
</tr>
<tr>
<td>IgA</td>
<td>98 (29.8)</td>
<td>23 (24)</td>
<td></td>
</tr>
<tr>
<td>Light-chain only</td>
<td>29 (8.8)</td>
<td>30 (32)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Others</td>
<td>7 (2.1)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>10 (3.0)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Light-chain type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\kappa$</td>
<td>165 (50.2)</td>
<td>38 (40)</td>
<td></td>
</tr>
<tr>
<td>$\lambda$</td>
<td>137 (41.6)</td>
<td>48 (51)</td>
<td>.11</td>
</tr>
<tr>
<td>Unknown</td>
<td>27 (8.2)</td>
<td>8 (9)</td>
<td></td>
</tr>
</tbody>
</table>

*Values are number (percentage) unless otherwise indicated.
†To convert creatinine level from micromoles per liter to milligrams per deciliter, divide micromoles per liter by 88.4.
‡To convert calcium level from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.25.

Renal failure is a critical prognostic factor in MM that is found in about 20% of patients at diagnosis.1,4 The basic pathogenetic lesion leading to renal failure is the so-called myeloma kidney caused by light-chain cast nephropathy.1,17 The incidence and the degree of renal failure varies considerably from one series to another because of the differences between the populations included in the studies and the criteria used to define renal failure. In our series from a tertiary hospital, 22.2% of patients with MM had a serum creatinine level of 177 µmol/L or greater ($\geq 2$ mg/dL) at diagnosis. In another large series4 from a single institution using the same definition for renal failure, the incidence of renal insufficiency was 18%, whereas in a recently reported multicentric study4 in which the creatinine limit to define renal failure was 133 µmol/L (1.5 mg/dL), its frequency was 31%.

Renal failure often seems to be a manifestation of high tumor mass myeloma. Renal failure is correlated with high light-chain urine protein excretion, extensive bone destruction with the associated hypercalcemia, a high serum lactate dehydrogenase level, and anemia partially resulting from destruction with the associated hypercalcemia, a high serum lactate dehydrogenase level, and anemia partially resulting from

Data on the reversibility of renal function in MM are controversial. When defining renal function recovery as a decrease in the serum creatinine level to less than 133 µmol/L ($< 1.5$ mg/dL) is required, the reversibility rate ranges from 20.5% to 55%.6,8,18-20 In our series, 26% of patients recovered normal renal function. Only 8% of our patients with severe renal failure (ie, serum creatinine levels $\geq 354$ µmol/L [≥4 mg/dL]) recovered renal function. In this sense, in 34 of the 94 patients from this series, renal replacement therapy with dialysis was necessary.9 As reported by other authors,21,25,27,28 the recovery rate in patients with renal failure severe enough to require dialysis was low in our series.9 In contrast, in about half of the patients with a serum creatinine level lower than 354 µmol/L (<4 mg/dL), renal function impairment was completely reversible. In fact, in the logistic regression analysis, factors associated with renal function recovery were serum creatinine level ($< 354$ µmol/L [<4 mg/dL]), amount of proteinuria ($< 1$ g/24 h), and serum calcium level ($\geq 2.88$ mmol/L [≥11.5 mg/dL]). Patients with a lower degree of renal failure, less proteinuria with damage to the renal tubules, and reversible hypercalcemia as a major cause for the renal failure were most likely to have reversible renal failure. The effect of the degree of renal failure on reversibility has also been demonstrated by others.3,7 However, in other studies6,18 including smaller
numbers of patients, no correlation was found between serum creatinine level and reversibility of renal function. In the series by Alexanian et al., the frequency of patients with hypercalcemia, as estimated from the results, was higher than in our study (57% vs 38%). This fact, and the lower proportion of patients with advanced renal failure requiring dialysis, probably accounted for the higher reversibility rate (51%) observed in the above-mentioned series. As in another large study, the average time to renal function normalization was less than 2 months, and only 2 patients required more than 4 months to recover renal function.

Little information is available on the response to therapy in patients with MM and renal failure. In 3 studies,19,24,27 the response rate ranged from 43% to 50%. In our series, the 39% response rate is significantly lower than the 56.4% response rate observed in patients with normal renal function. However, the lower response rate in patients with renal failure is because 30% of them died within the first 2 months of diagnosis compared with early death of only 7% among patients with normal renal function. Indeed, if patients dying during the first 2 months after starting treatment are excluded, the response to therapy is similar irrespective of whether they had impaired renal function. Thus, renal failure by itself does not imply resistance to chemotherapy.5 Our results concerning response rate are similar to those reported by Alexanian et al.3 These authors, using the Southwest Oncology Group criteria, found that slightly more than one third of their patients responded to chemotherapy. The response rate in patients given combination chemotherapy was significantly higher than that of those receiving a single alkylating agent plus prednisone. This is in agreement with the results of most myeloma trials.39,30

In patients with MM and renal failure, the reported median survival ranges from 4 months to slightly more than 1 year.3,7,18-20 The median survival of approximately 9 months observed in our patients is within this range. Unfortunately, the high mortality rate of approximately 30% within the first 2 months of diagnosis is still a constant finding in patients with MM and renal failure,1,18-20,31,32 which results in the short median survival observed in all the series. It has been stressed that in patients with renal failure, cycles of melphalan and prednisone are not the most appropriate treatment because the need for dose adjustment of melphalan to avoid severe myelosuppression may imply the risk of suboptimal treatment.33,34 Conversely, combination chemotherapy could produce a more rapid response with a faster reduction in light-chain protein production, thereby avoiding further renal damage.34,35 However, as in a general myeloma series,36 the survival of our patients treated with single alkylating agents plus prednisone was similar to that of those treated with combination chemotherapy. It also has been suggested that chemotherapy with a 4-day continuous infusion of VAD could be better than more conventional treatments in patients with MM and renal failure. However, this notion has not been investigated in prospective trials. Patients with renal failure are usually excluded from high-dose therapy followed by

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Table 2. Multivariate Logistic Regression Analysis of Features Associated With Reversibility of Renal Failure

<table>
<thead>
<tr>
<th>Feature</th>
<th>Relative Risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine level &lt;354 µmol/L</td>
<td>7.5 (2.28)</td>
<td>.001</td>
</tr>
<tr>
<td>Calcium level &gt;2.88 mmol/L</td>
<td>3.27 (1.1-9.3)</td>
<td>.02</td>
</tr>
<tr>
<td>Urine proteins &lt;1 g/24h</td>
<td>2.78 (1.09-7.08)</td>
<td>.02</td>
</tr>
</tbody>
</table>

*To convert creatinine level from micromoles per liter to milligrams per deciliter, divide micromoles per liter by 88.4.
†To convert calcium level from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.25.

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Figure 1. Survival curves of 94 patients with renal failure vs 329 patients with normal renal function (median, 8.6 vs 34.5 months; P < .001).

Figure 2. Survival curves of 24 patients who recovered renal function vs 67 patients with nonreversible renal failure (median, 28.3 vs 3.8 months; P < .001).

Figure 3. Survival curves of 329 patients with initial normal renal function vs 24 patients who recovered renal function (median, 34.5 vs 28.3 months; P = .97).
stem cell rescue. However, results of a recent study show that high-dose melphalan pharmacokinetics is not affected by renal function impairment. Moreover, the results of autotransplantation in 23 patients with MM and renal failure showed that in patients with renal insufficiency toxic effects, kinetics of engraftment and even-free survival were comparable with those observed in patients with normal renal function. However, overall survival was shorter in patients with renal failure, and normalization of renal function occurred in 4 (17%) of 23 patients. It has been suggested that rapid removal of light chains with chemotherapy and plasmapheresis could prevent irreversible renal failure. In a randomized trial, plasmapheresis and chemotherapy decreased the serum M-protein more rapidly than chemotherapy alone. However, when severe myeloma cast nephropathy is already present, plasmapheresis is unlikely to be of benefit. In the experience of Torra et al, plasmapheresis was not helpful in patients with renal failure severe enough to require dialysis. A program of VAD chemotherapy plus plasma exchange with serial measurements of the light chains in patients with acute severe renal failure still not requiring dialysis is going to be started. In contrast to the results reported in other series, the survival of patients who recovered normal renal function was significantly longer than that of those with nonreversible renal failure. More important, perhaps, survival in the latter patients was not different from that of patients with normal renal function. Whereas in some studies, no correlation between survival and the degree of renal function was found, the severity of renal failure was an independent prognostic factor in our series. The most important prognostic factor associated with significantly longer survival was response to chemotherapy. Response to treatment was recognized as the most significant prognostic factor in a previous study of our overall myeloma series and also has been associated with a highly significant survival benefit in a series of patients with MM and renal survival. In summary, in our series, almost one fourth of the patients with MM had renal failure at diagnosis. About 40% of the patients responded to chemotherapy, and the factors associated with renal function recovery were degree of renal failure (serum creatinine level, < 354 μmol/L (<4 mg/dl)), presence of hypercalcemia (calcium level, ≥ 2.88 mmol/L (≥11.5 mg/dl)), and amount of proteinuria (< 1 g/24 h). Response to chemotherapy and the severity of renal failure were the only independent prognostic factors associated with significantly longer survival.

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REFERENCES