Reversal of acute renal failure by bortezomib-based chemotherapy in patients with multiple myeloma

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ABSTRACT

Paraprotein induced renal failure is a frequent complication of multiple myeloma and is associated with poor survival. Previously, reversal of renal function has been hampered by the lack of fast acting and highly effective myeloma therapy and most patients remained or became dependent on hemodialysis. Here we show reversal of acute paraprotein-induced renal failure by bortezomib-based therapy in 5 out of 8 patients. Improvement of renal function was preceded by a significant reduction in paraprotein concentration in all patients, with improvement in renal function.

Key words: acute paraprotein-induced renal failure, multiple myeloma, nephrotoxic light chains, bortezomib, hemodialysis.

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Mild to moderate renal impairment is a common complication of multiple myeloma and found in about one fourth of patients at time of diagnosis.[1,2] It evolves in up to 50% of patients during the further course of their disease. Frequently, hypercalcemia, nephrotoxic drugs, infections, dehydration and hyperuricemia lead to mild to moderate renal impairment but recovery of renal function can usually be achieved by eliminating these pathogenic factors. In about 10% of patients, severe and often permanent renal dysfunction develops with most of these patients becoming dependent on chronic hemodialysis. The main cause of permanent renal failure is excessive production of nephrotoxic monoclonal light chains. These proteins enter renal tubuli after passage through the glomerular apparatus leading to overloading of the endocytic process of the proximal tubuli and initiating a stress response. This response includes phosphorylation of MAPKs and nuclear transcription factors NF-κB with ensuing production of inflammatory and proinflammatory cytokines, such as TNF-α, interleukin-6, 8, and monocyte chemo-attractant protein-1.[3] This finally results in apoptosis of tubular lining cells with accumulation of cell debris, tubular cast formation, tubular obstruction, distension and dysfunction. If this process is not interrupted fast enough, renal impairment becomes irreversible and chronic hemodialysis mandatory for the rest of the patient's life. High-dose treatment with autologous stem cell transplantation has the potential of a rapid and significant reduction in light chain production.[4] But this procedure is limited to patients who are suitable for this aggressive therapy and is often hampered by the lack of pre-stored stem cells. Conventional chemotherapy of multiple myeloma induces remission in about two thirds of patients, but time to remission usually takes too long and remissions are mostly incomplete. Therefore, a decrease in monoclonal light chains is neither fast enough or sufficient, resulting in a low reversal rate of acute myeloma-induced renal failure.[5]

The introduction of bortezomib, thalidomide and lenalidomide in the treatment of patients with multiple myeloma has widened the options available for therapy. We report the use of bortezomib-based treatment in patients with acute renal failure with the intention to achieve a rapid reduction of light chains and to reverse renal impairment.

Design and Methods

Eight patients were included in the study. Seven had newly diagnosed and 1 patient previously treated and subsequently progressive myeloma presenting with acute renal failure defined by a glomerular filtration rate <20 mL/min.. Diagnosis of myeloma induced renal failure was established after clinical exclusion of pathogenic factors other than light chain proteinuria. Twenty-four hour proteinuria and urine protein electropheresis, immunofixation or determination of free light chains was available in all patients but renal biopsies were not performed. Response to myeloma therapy was evaluated according to the EBMT criteria.[6] We also included 2 other categories: near-complete response (nCR), defined as no detectable paraprotein by electrophoresis with positive immunfixation, and very good partial remission (VGPR), defined as greater than 90% reduction in serum or urine paraprotein. Patient characteristics are shown in Table 1.

Patients with poor performance status (ECOG 3-4) or age >70 years received bortezomib 1.0 mg/m^2 on days 1, 4, 8 and 11 of a 21-day cycle. All other patients received 1.3 mg/m^2 bortezomib. Dexamethasone 20 mg was added in 3 patients on the day of bortezomib and the day after, and 3 patients received in addition doxorubicin 9 mg/m^2 on the same days as bortezomib therapy. Two patients received only 3 chemotherapy cycles, one because of progressive disease and one in conformance with patient's wishes.

Table 1. Patients' characteristics.

Presenting features	
Age (years), median (range)	63.5 (47-77)
Sex (male/female)	7/1
Stage IIB/IIIB	1/7
Paraprotein	
λ light chain only	4
κ light chain only	1
IgG κ	3
Initial creatinine (mg/mL), median (range)	9.05 (5.2-12.0)
Hemodialysis	5
Treatment	
Bortezomib (B)	2
B+Dexamethasone (Dex)	3
B+Dex+Doxorubicin	3
Treatment response	
Renal	
Creatinine ≤ 2 mg	2
Creatinine < 3 mg	3
Myeloma	
CR, nCR	3
VGPR	1
PR/PR* transient	1/1
MR*/PD*	1/1

*Patients without renal response.

Results and Discussion

Five out of the 8 patients with acute myeloma induced kidney failure experienced reversal of renal failure. Their median creatinine level decreased from 9.05 mg/dl (5.2-12.0 mg/dL) to 2.1 mg/dL (0.8-2.4 mg/dL). Time to creatinine concentration of ≤2 mg/ml was 44 and 48 days in the 2 patients with excellent results. In the other 3 responding patients, the lowest creatinine levels achieved were 2.1 mg/dL, 2.3 mg/dL and 2.4 mg/dl respectively, and the time to these levels was 41, 71 and 71 days respectively. All patients with significant improvement of renal impairment achieved objective tumour response with 3 patients achieving CR or nCR, 1 patient achieving VGPR, and 1 patient reaching PR. Median time to response (PR or >PR) of myeloma was 43 days. Only 1 of the 3 renal non-responders achieved a transient PR after cycle 2, but relapsed before cycle 5. One patient had a MR and one PD. After a median follow-up of 15.9 months four patients died, two renal non-responders from progressive myeloma and two patients with initial renal and tumour response from pneumonia and subsequent relapse, respectively. Our intention was to start treatment as soon as possible after confirmation of the diagnosis of myeloma paraprotein-induced renal failure and the exclusion of other causes of renal failure, such as nephrotoxic drugs, hypercalcemia, hyperuricemia, dehydration and sepsis to reduce the risk of irreversible cast nephropathy.

The accuracy of diagnosis without histologic proof by kidney biopsies is supported by the subsequent recovery of renal function with the decrease of myeloma proteins in the 5 responding patients. Indeed, complete or significant reduction of the nephrotoxic paraproteins seems to be the decisive pre-condition for recovery of renal function with regeneration and proliferation of residual tubular cells.[7] The role of plasmapheresis as a means of reducing toxic light chains has been investigated in 3 prospective randomized trials.[8-10]

In 2 of them, including the largest with 97 patients, no benefit was noted.[8,9] Recently, a specific hemodialysis membrane has been used for more effective removal of circulating light chains. This led to reversal of renal failure in 3 out of 5 patients.[11] However, the real benefit of this procedure remains to be determined.

Conventional chemotherapy with its low rate of complete response is infrequently associated with

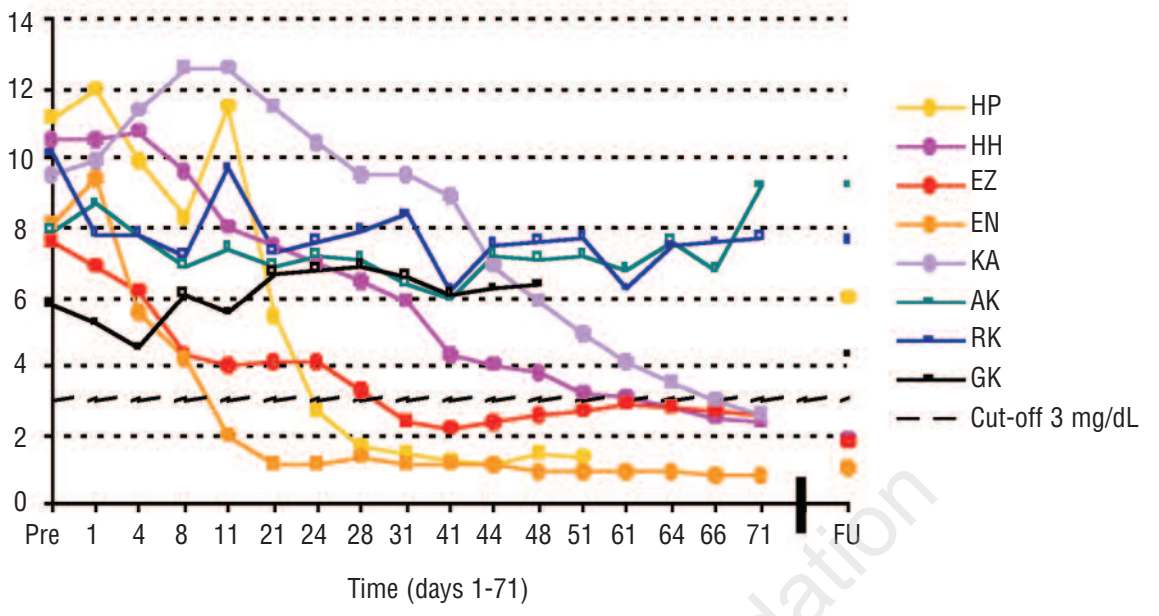

Figure 1. Creatinine values during bortezomib or bortezomib-based therapy.

improvement of renal failure.[5] High dose therapy with melphalan 140 mg/m^2 is an option for younger and physiologically fit patients. This treatment has been shown to induce dialysis-independence in 24% of patients who were hemodialysis dependent while receiving high dose therapy. In spite of its activity, many myeloma patients with severe renal failure will not agree to this aggressive therapy.[4]

Bortezomib-based combination treatment with dexamethasone,[12] or with the addition of doxorubicin[13] or with melphalan-prednisone,[14] has been shown to be highly effective and to rapidly induce tumour response. This makes it an excellent choice for such an emergency situation. The time to response of single agent bortezomib therapy was only 38 days in pre-treated patients.[15] A further argument for the use of bortezomib in myeloma kidney disease derives from its potent inhibitory activity of NFκ-B. This transcription factor is strongly activated in renal tubular cells of proteinuric patients[16] and inhibition of NFκ-B has been shown to significantly reduce inflammation and fibrosis in an experimental model of glomerulonephritis.[17]

Bortezomib, therefore, may directly reduce inflammation in myeloma kidney disease and may contribute to improvement in renal function. Bortezomib has previously been shown to be equally effective in 10 patients with renal insufficiency compared with patients with normal renal function.[18] Toxicity was not increased in the former cohort probably because plasma elimination of bortezomib is independent of renal function. Similar findings were reported in a retrospective study of 24 patients with pre-treated myeloma on chronic hemodialysis.[19] Single agent bortezomib treatment or in combination with dexamethasone, thalidomide and/or doxorubicin, yielded an overall response rate of 75%, with 30% complete or nCR and 45% PR. In spite of chronic treatment with hemodialysis, bortezomib-based chemotherapy was well tolerated. Recently, in a small series of 4 patients, reversal of renal failure was reported in all of them after 1 to 2 cycles of bortezomib or bortezomib-dexamethasone treatment.[20]

In conclusion, the improvement of renal function with bortezomib-based therapy obtained in 5 out of 8 patients with paraprotein induced acute renal failure gives rise to the hope that, in the future, more patients with this severe complication may be salvaged by bortezomib-based or other effective myeloma therapy.

Authors' contribution

HL, JD, HG, AL and JGM contributed patients' data and revised the manuscript. Data were collected and analyzed by HL, who produced the draft.

Conflicts of Interest

HL has participated in advisory board meetings and educational events of Janssen-Cilag and Ortho Biotech: JD has participated in advisory board meetings and educational events of Janssen-Cilag and Ortho Biotech; HG, AL and JM have no potential conflict of interest relevant to this paper to disclose.

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